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A PRELIMINARY REPORT ON SOME CASES OF CONTRACTED KIDNEY

By S. C. DYKE

(From the Clinical Units, St. Thomas's Hospital)

With Plates 1 and 2

Introduction.

IN spite of a continuous stream of literature from the time of Bright to the present day, the bases of differentiation of the various types of contracted kidney remain far from being well defined. The earlier attempts at classification on macroscopic appearances have long been admitted to be entirely inadequate, though such is the power of tradition that the medical student of to-day still distinguishes the 'red' from the 'white' kidney and ascribes some aetiological significance to such a distinction. The clearest and most satisfactory pathological classification of all forms of nephritis, those associated with contracted kidneys among the others, available in English up to the present was worked out by Gaskell (1) in 1912. The criteria established by Gaskell for his classification were almost purely histological; in the present study eight cases of nephritis associated with contracted kidney are considered; in all of these observations were made during life upon the renal function, and the microscopical condition of the kidneys was investigated after death. The kidneys examined form part of a series of about 100 taken more or less at random from post-mortems after death from various causes; they represent the only cases, in the series showing contracted kidneys, in which tests of renal function had been carried out during life. The remainder of the series served, in a manner, as controls for the normal and for morbid conditions other than those under immediate consideration. For purposes of comparison a report is included on one case (71) in which the kidneys, although showing changes closely allied to those under consideration, were not contracted but of normal size.

Cases.

Case 76. Male, aged 79. Admitted 24.12.21. Complained of difficulty of micturition, and passage of blood in the urine for the past twelve months; for two weeks there had been pain on micturition. On admission the prostate was found to be greatly enlarged. 28.12.21. Suprapubic cystotomy performed.

[Q. J. M., Oct., 1922.]

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3.12.2. Blood urea, 64 mg. per cent.

Urea in 24 hrs. specimen, 2.6 per cent.

Urea in urine after 15 grm. urea by mouth : 1st hour, 2.6 per cent. ;
2nd hour, 2.3 per cent.

The patient became weak and his mind wandered a good deal. Pus in urine. Irregular pyrexia.

17.1.22. Blood urea, 60 mg. per cent.

Urea in 24 hrs. specimen, 1.55 per cent.

Urea in urine after 15 grm. urea by mouth : 1st hour, 1.6 per cent. ;
2nd hour, 2.55 per cent.

2.2.22. Blood urea, 64 mg. per cent.

Urea in urine after 15 grm. urea by mouth : 1st hour, 1.78 per cent. ;
2nd hour, 2.15 per cent.

22.2.22. Died quietly, apparently from cardiac failure due to toxæmia.

At post-mortem.—No peritonitis or extravasation of urine; mucous membrane of bladder dark grey, thick, and sloughing; left ureter dilated; left septic pyelonephritis. Left kidney $3\frac{1}{2}$ oz., right $3\frac{1}{2}$ oz. Heart weight $11\frac{1}{2}$ oz. Aorta very atheromatous. Attached to the left kidney was a large circumscribed growth, not invading the kidney nor any other tissues, which proved on section to be a hypernephroma.

Histology of kidney. Framework shows a general diffuse fibrosis; in parts, particularly under the capsule, this is fairly dense; it is accompanied in certain areas by some slight degree of round-celled infiltration, but this is not a marked feature. The tubules, particularly in the labyrinth, show signs of cloudy swelling, but the nuclei stain well, and there seems to be no actual degeneration; some contain fat droplets; on the whole, the tubules are not greatly interfered with by the fibrosis, nor are they greatly dilated. Many of the glomeruli, particularly in the denser areas of fibrosis, show atrophy and fibrosis; many of these atrophic glomeruli show faint fat staining, elsewhere the glomeruli appear fairly normal. The larger vessels show intimal hyperplasia, without fat change, with thickening of the adventitia and splitting of the internal elastic lamina. The arterioles show no intimal change.

Case 8. Male, aged 50. In 1911, operation for removal of vesical calculi; 1913, stricture with perineal fistula; internal urethrotomy and sounds; re-admitted 12.7.20, complaining of painful and difficult micturition; no evidence of stone; *B. coli* in urine. Readmitted 12.8.20, complaining of painful and frequent micturition with hæmaturia for four weeks. On admission, urine: albumin ++, sp. gr. 1006. No evidence of stone.

Blood urea, 93 mg. per cent.

Urea in 24 hrs. specimen of urine, 0.9 per cent.

Died 25.8.20.

At post-mortem.—Kidneys cystic and fibrosed, left 1 oz., right 4 oz. No remarks as to condition of other organs.

Histology of kidneys. General increase in fibrous tissue, this being particularly marked in the form of dense bands running radially to the capsule; in these areas is some round-celled infiltration, but this is not a prominent feature. In the fibrosed areas the tubules are distorted; between the areas of fibrosis they show no great change from normal. The glomeruli show gross alterations, few absolutely normal ones being present in any section; many of them are hypertrophied, and of these many show degenerative changes in the tuft, as evidenced by the presence of hyaline change and fat. Many show thickening, apparently fibrous, of the capsule; these are mostly small and atrophic; others show proliferation both of the tuft and of the capsule. The larger vessels show intimal proliferation but no fat change; the arterioles show some fat change in the intima along with hyperplasia.

Case 23. Female, aged 53. Admitted 8.12.20, complaining of headache, pain in the side of the face, and diplopia. First attack of a like nature took place 20, and second 15 years ago. For the last six months there had been headache and vomiting. The arteries were tortuous and thickened; blood-pressure $\frac{24}{15}$. Albuminurea marked. 13.12.20. Flame-shaped haemorrhages present in retina.

13.12.20. Blood urea, 67 mg. per cent.

13. 1.21. " " 92.5 mg. per cent.

31. 1.21. C.S.F. " 250 mg. per cent.

3. 2.21. Died.

At post-mortem.—Heart: left ventricle greatly hypertrophied; weight of organ $14\frac{1}{2}$ oz., atheroma of aorta. Kidneys: right $4\frac{3}{4}$ oz., left 5 oz.; some reduction of cortex, tough; capsule strips fairly well, but leaves a granular surface. Brain: oedema of pia arachnoid, considerable sclerosis of cerebral vessels, one small haemorrhage at right side of pons at level of 5th nerve.

Histology of kidneys. Very similar to Case 8; round-celled infiltration not a prominent feature, though quite evident; the glomerular changes are as described above; intimal hyperplasia of the larger vessels and intimal hyperplasia with fat change of the arterioles are very marked.

Case 41. Male, aged 44. Admitted 20.4.21. History of headache for two years; for six months, vomiting with no relationship to food; some polyuria. On admission, arterio-sclerosis; blood-pressure $\frac{21}{15}$; white patches in both retinae; urine, sp. gr. 1012; albumin + +.

28.4.21. Blood urea, 492 mg. per cent.

Urea concentration in 24 hrs. specimen urine, 1.35 per cent.

2.5.21. Died.

Post-mortem findings not available.

Histology of kidneys. Changes as in the preceding cases; the fibrosis is very dense, particularly in the areas disposed radially to the capsule; in these areas the tubules have almost disappeared; between them the tubules retain their normal arrangement but are greatly dilated. Round-celled infiltration is present, being particularly marked in the areas of dense fibrosis. The hyperplasia and fatty change of the intima of the arterioles are extreme.

Case 44. Male, aged 11. Admitted 19.4.21. No history of ill health up to fourteen days before admission, when he developed a septic sore on one finger. Thereafter suffered from vomiting and abdominal pain; vision became blurred, and later there was some oedema of the face. Some haematuria. On admission there was no oedema; the apex beat was in the sixth space in the middle line, aortic systolic bruit at right sternal edge; blood-pressure $\frac{120}{80}$. Urine contained albumin and red cells.

22.4.21. Blood urea, 106 mg. per cent.

11.5.21. " " 241 " "

13.5.21. Death in uraemia.

At post-mortem.—Kidneys: right $1\frac{1}{4}$ oz., left $3\frac{1}{4}$ oz., both very fibrous; capsule thick and stripping with difficulty; surface showed deep scarring, together with granulation and multiple punctate haemorrhages; pelvic fat increased; differentiation between cortex and medulla lost. Heart $9\frac{1}{4}$ oz. Left ventricle greatly hypertrophied but not dilated. Aorta: intense atheroma, particularly of the abdominal portion.

Histology of kidneys. Characteristic hyperplasia. Fatty change of the arterioles is present to a very remarkable degree; the larger arteries show intense intimal hyperplasia without fat. There is a great increase of fibrous tissue, of which the radial distribution is very apparent; in the areas of fibrosis is an intense round-celled infiltration, and the tubules are damaged and atrophied; between these areas round-celled infiltration is almost absent, and the tubules

are greatly dilated and show flattening of the epithelium. The glomeruli are greatly altered; in the areas of fibrosis they are small and atrophic, elsewhere they are greatly hypertrophied and show hyaline and fatty change with disintegration of the tuft, also proliferation of the endothelium lining both the tuft and capsule; many show haemorrhage into the tuft.

Case 50. Female, aged 63. Admitted 12.5.21, with history of oedema of legs and trunk, occurring in attacks for the last two years. On admission, heart enlarged; urine, sp. gr. 1009; albumin ++; no blood in urine.

19.5.21. Blood urea, 96 mg. per cent.

Urea concentration in urine after 15 grm.: 1st hour, urea 0.98 per cent.; 2nd hour, urea 1.25 per cent.

6.6.21. Rigor: temperature 102°, pain in chest.

11.6.21. Died.

At post-mortem.—Kidneys: right 3½ oz., left 2¾ oz., small, red and fibrosed; differentiation between cortex and medulla lost; pelvic fat increased; capsule strips with difficulty, leaving coarsely granular surface. Heart enlarged. Thickening with vegetations of aortic and mitral valves. Aorta atheromatous.

At apex of right lung was a large septic infarct, and several infarcts were present in the spleen.

Histology of kidneys. Intense fibrosis with the usual radial distribution; round-celled infiltration is present, but is not a marked feature; in a zone between the medulla and cortex the thickened fibrous framework shows an intense degree of hyaline and fatty change in which scarcely any tubules are to be seen. The arterioles show characteristic hyperplasia and fatty change of the intima; the larger arteries as usual show hyperplasia alone. In the fibrosed areas the tubules have almost disappeared; between these areas they show dilatation and flattening of the epithelium. The glomeruli show changes of an atrophic rather than of a proliferative nature; hypertrophy of the glomeruli, though present, is not marked; endothelial proliferation was not observed.

Case 58. Male, aged 38. Admitted 9.6.21, with four months' history of palpitation, dyspnoea, dyspepsia, and lumbar pain. No oedema. On admission, pale; apex beat in fifth space three and a half inches from left sternal edge; urine, sp. gr. 1010, albumin ++. Wassermann reaction negative.

13.7.21. Oedema of ankles; dyspnoea; granular casts in urine.

17.7.21. Increasing oedema.

12.8.21. Intense oedema.

9.6.21. Blood urea, 68 mg. per cent.

8.8.21. " " 89 " " "

13.9.21. Died.

At post-mortem.—Kidneys very hard and tough, deeply congested; differentiation between cortex and medulla lost; capsule strips intact, leaving finely granular surface; pelvic fat increased. Heart greatly hypertrophied, particularly on the left side; muscle shows numerous pale areas of degeneration. Aorta: general nodular atheroma; no evidence of fibrosis; no calcification.

Histology. Kidneys show fibrosis in the usual radial distribution with intervening more or less unaffected areas: some round-celled infiltration, very local in distribution, is present in the fibrotic areas. The tubules are much as in Case 44. The glomeruli show both atrophic and hypertrophic changes, proliferation of the endothelium being marked. The arterioles show the characteristic hyperplasia and fatty change of the intima; the larger vessels hyperplasia alone. The same vascular changes are present in the spleen. The aorta shows intimal hyperplasia with fatty change and also some fat in the media. The heart-muscle shows areas of a peculiar degeneration characterized by fragmentation of the fibres, which in these areas stain deeply with connective-tissue dyes, such as aniline blue and acid fuchsin, and also with methylene blue. The fibrous tissue is increased and contains fat.

Case 79. Male, aged 33. Admitted 23.1.22, complaining of headache and vomiting since June 1921; epistaxis occasionally since same date. Since December 1921 there had been swelling of the face. On admission patient was very pale; urine contained albumin; blood-pressure $\frac{180}{120}$.

25.1.22. Blood urea, 306 mg. per cent.

Urea concentration in urine 0.75 per cent. After 15 grm. urea by mouth, 1st hour, blood urea 370 per cent., urine urea 0.85 per cent.; 2nd-hour, blood urea 430 per cent., urine urea 0.75 per cent.

4.2.22. Albuminuric retinitis in both disks.

16.2.22. Wassermann reaction negative.

12.3.22. Died.

At post-mortem.—The heart was greatly hypertrophied, weight $16\frac{1}{2}$ oz.; pericardium contained a great excess of fluid. Lungs oedematous. Both kidneys were of the typical 'small white' description; very dense and fibrous and apparently containing very little blood; the capsule stripped with difficulty, leaving a granular surface; weight, right and left, $3\frac{1}{2}$ oz.

Histology of the kidneys. There is a general intense fibrosis throughout the whole organ; this is so nearly universal that it is difficult to make out the radial arrangement remarked in the previous cases; this is, however, indicated by the persistence of small triangular areas of unfibrosed tubules near the capsule, having their apex towards the medulla. Throughout the fibrous tissue is a general and fairly intense round-celled infiltration. The tubules are constricted and distorted by the fibrosis; some are dilated and show flattening of the epithelium; many show fat in the epithelial cells and fatty casts in the lumina. The glomeruli are universally affected; no normal ones are to be seen; the majority are smaller than normal, and many show fibrosis and hyaline change; many are reduced to a small homogeneous disk containing a few nuclei and some fat. Others of the glomeruli show hypertrophic and inflammatory change—these are larger than normal but show various stages of disintegration of the tuft, with fatty change, endothelial proliferation, and adhesions between capsule and tuft. The larger vessels show some intimal proliferation with splitting of the internal elastic lamina; the smaller ones show in a high degree the characteristic hyperplasia and fatty change of the intima.

Case 71. Male, aged 27. Admitted 27.11.21, with six years' history of occasional headache and vomiting. Discharged from Army for 'debility' in 1916. Kidney disease diagnosed in 1917. For last six weeks headache and vomiting; some frequency of micturition, slight oedema. On admission cyanosed and dyspnoeic; urine, sp. gr. 1010; blood-pressure $\frac{135}{110}$.

28.11.21. Blood urea, 380 mg. per cent.

Urea in 24 hrs. specimen, 1.28 per cent.

30.11.21. Increased cyanosis; death from cardiac failure.

At post-mortem.—Kidneys normal in size: right 5 oz., left 5 oz.; cortex reduced; both cortex and medulla congested, suggesting subacute attack in diseased kidney. Liver nutmeg. Spleen large and congested and showing perisplenitis. Lungs fibrosed as result of back pressure. Heart 20 oz.; hypertrophied, especially the left ventricle; right ventricle dilated; no valvular lesion. Aorta atheromatous.

Histology of kidneys. Very great increase in fibrous tissue; this increase is more general than in the cases considered above; round-celled infiltration is very intense, the collections of such cells in places almost giving rise to the appearance of abscesses, were such possible in the absence of polymorphonuclear cells. The glomeruli are grossly affected; many are smaller and many larger than normal; the smaller show fibrosis to the point of complete disappearance; the larger show proliferation of the endothelium and hyaline change of the tuft. Fat is present to a slight degree in many glomeruli of all sizes. The arterioles do not show the characteristic intimal hyperplasia and fatty change described in the preceding six cases.

Discussion.

Consideration of the above histological reports makes it evident that the departures from normal in the kidneys may be grouped under three heads. In the first place are the atrophic or recessive changes, such as interstitial fibrosis, and shrinkage and fibrosis of the glomeruli; secondly, are the inflammatory and hypertrophic changes, such as round-celled infiltration, hypertrophy of the glomeruli, and proliferation of the endothelium both of glomerular capsule and tuft; thirdly, there are the vascular changes, intimal hyperplasia both of the arteries and arterioles, together with fatty change in the latter.

It is mainly on the basis of these histological changes that contracted kidneys have in the past been differentiated into two main groups—the secondary and primary; the former supposedly representing the final result of a long-continued inflammatory process or of a repeated succession of short attacks, while the latter is presumed to be the result of arterio-sclerosis of the proper vasculature of the kidney, leading to interference with the blood supply, with consequent fibrosis and contraction.

This second class, that of the primary cardio-vascular contracted kidney, has been clearly divided by Gaskell into two subdivisions very different in their aetiology. In the first subdivision he places those kidneys in which the changes are mainly atrophic or recessive with little evidence of inflammation; the larger vessels of such kidneys showed intimal hyperplasia without fat change, often accompanied by thickening of the media; the arterioles are unaffected; in fact, the vascular changes are those of senile arterio-sclerosis. This type is usually associated with a heart of normal or small size, and with a low blood-pressure during life. A sharp distinction must be made between the preceding and the second subdivision of the primary contracted kidney. In this second class the most prominent change is an intense intimal hyperplasia with fatty change confined to the smaller arteries and the arterioles; the larger vessels show intimal hyperplasia indistinguishable from that seen in the preceding class, but the fat change is strictly confined to the smaller branch arteries and arterioles: where sections are made so as to cut the point of issue of small branch arteries from a larger trunk the sudden appearance of the fat at the point of junction is most marked (Plate 1, Fig. 2). In this type round-celled infiltration and other evidences of inflammation are present to a greater or less degree. This type is always associated with a hypertrophied heart and a high blood-pressure during life.

This hyperplasia of the intima of the arterioles with fatty change, when present, is not confined to the kidneys. This was noted by Gull and Sutton (2) (1872), who in their classical paper described the condition under the name of arterio-capillary fibrosis; they, however, failed to differentiate between it and senile arterio-sclerosis. Evans (3) (1921), who investigated and described the condition very fully under the name of 'diffuse hyperplastic sclerosis', laid great stress on the widespread nature of the changes in the arterioles.

Thus three types of contracted kidney have been described :

- (1) Secondary to inflammatory processes.
- (2) Primary cardio-vascular :
 - (a) Senile arterio-sclerotic ;
 - (b) Diffuse hyperplastic sclerotic.

The senile arterio-sclerotic type of the primary cardio-vascular contracted kidney is represented in pure form only by Case 76 of the present series. In this the atrophic changes dominate the picture ; there is fibrosis and obliteration of glomeruli without much evidence of inflammation. Case 50 shows changes of the same nature, but in combination with more active inflammatory processes. The biochemical findings in this latter case cannot then be looked upon as representative of this type of change, as they can be in Case 76. In this latter case, up to shortly before death there was no departure from the normal in the biochemical test results. Death was apparently due to toxæmia from the infected bladder and not to the renal condition.

It remains now to distinguish between the second subdivision of the primary (2 *b* above) and the secondary contracted (1 above) kidneys, and here difficulties arise. Gaskell, in describing his secondary contracted kidney, pointed out that hyperplasia and fatty change of the intima of the arterioles were often present, and his descriptions of this class and of his second subdivision of the primary cardio-vascular kidney are almost interchangeable. The association of the vascular with the inflammatory changes so impressed Evans that he regarded neither as primary, but both as results of the action of a common toxic agent.

In looking over the records of Cases 8, 23, 41, 44, 50, 58, and 79 above, it is evident that in all both inflammatory and vascular changes are present—in different degrees, it is true, but always to such an extent that neither can be ignored. In Case 23 the vascular features dominate the picture, but round-celled infiltration is present ; in Case 58 the reverse is the case ; in Cases 44 and 79 changes of both types are very markedly present. In none of these kidneys does it seem possible to say that either the inflammatory or the vascular lesion was primary ; the indications seem to be of the production of both as the result of the action of some unknown toxic agent. This, as pointed out by Evans, brings the hyperplasia of the intima of the arterioles into line with such other changes as the glomerular endothelial proliferation as the visible sign of reaction to an inflammatory process either of long standing or in repeated attacks. On any other view it is difficult to account for the state of affairs in Cases 44, 58, and 79, particularly in the first, where in a boy of 11 years of age, after an illness of only six weeks, both vascular and inflammatory changes are found in the kidneys, and both to a very marked degree.

Case 71 was included in the series as an example of a kidney showing only inflammatory change. As pointed out, the kidneys in this case were not contracted, but of normal size ; they belonged, in fact, to the traditional class of 'large white kidneys'. The history in this case plainly points to recurring attacks of inflammatory trouble over a long period, though not more plainly than in some of the

other cases. Why the vascular changes should have been absent in this kidney is not clear—it may be that the noxious agent was different from that in the cases where the vascular changes appeared—or, it may be that had life been prolonged these changes would have appeared in due course; that no great time is necessary for their development is evidenced by Case 44. In any case, it is interesting to note that in the absence of vascular changes, but with the inflammatory lesions present alone, contraction did not occur.

On histological grounds then, it would seem that although it is possible to identify definitely the primary contracted kidney associated with senile arterio-sclerosis, it is difficult to differentiate from the secondary contracted kidney that associated with the condition which, following Evans, may be described as 'diffuse hyperplastic sclerosis'.

The case is much the same when the results of the blood urea estimations taken during life are considered. The results of these tests are shown in tabular form below:

Case No.	Age.	Blood Urea. mg. %.	Days before death of per- formance of test.
8	50	93	Not stated
23	53	67	50
		92.5	20
		250	3
		(C. S. F.)	
41	44	492	5
44	11	106	21
		241	2
50	63	96	23
58	38	68	125
		89	35
79	33	306	47
71	27	380	2
76	79	64	51
		60	37
		64	22

In Case 76, that of contracted kidney associated with senile arterio-sclerosis, it will be noted that the blood urea shows no great departure from the normal. In all the remaining cases the available data indicate the same features—a moderate rise above the normal in the early stages of the disease with a progressive increase to a very great height before death.

Within limits the same may be said of urea concentration tests, either after the administration of 15 gm. of urea by mouth, or as observed on urine passed on hospital diet. Whereas in Case 76 the results of these tests indicate no gross impairment of function, in all the other cases in which such observations were made there is indication of a distinct failure in the excretion of urea.

Summary and Conclusions.

1. Eight cases of nephritis associated with contracted kidney are considered, and one in which the kidneys were not contracted.
2. One of the contracted kidneys showed changes associated with senile

arterio-sclerosis without evidence of inflammation; in this case biochemical tests performed during life showed no evidence of departure from normal.

3. The remaining seven contracted kidneys all showed a combination of an inflammatory process with intimal hyperplasia and fatty change in the arterioles of the type associated with 'diffuse hyperplastic sclerosis'. The biochemical tests in these cases showed a progressive debasement of renal function.

4. The one case of uncontracted kidney showed inflammatory changes without intimal hyperplasia of the arterioles.

5. On neither histological nor biochemical grounds was it possible to divide the kidneys referred to in paragraph 3 above into primary cardio-vascular or secondary inflammatory. It is suggested that both the inflammatory and the vascular changes of the type described as 'diffuse hyperplastic sclerosis' are the common results of the action of one toxic agent.

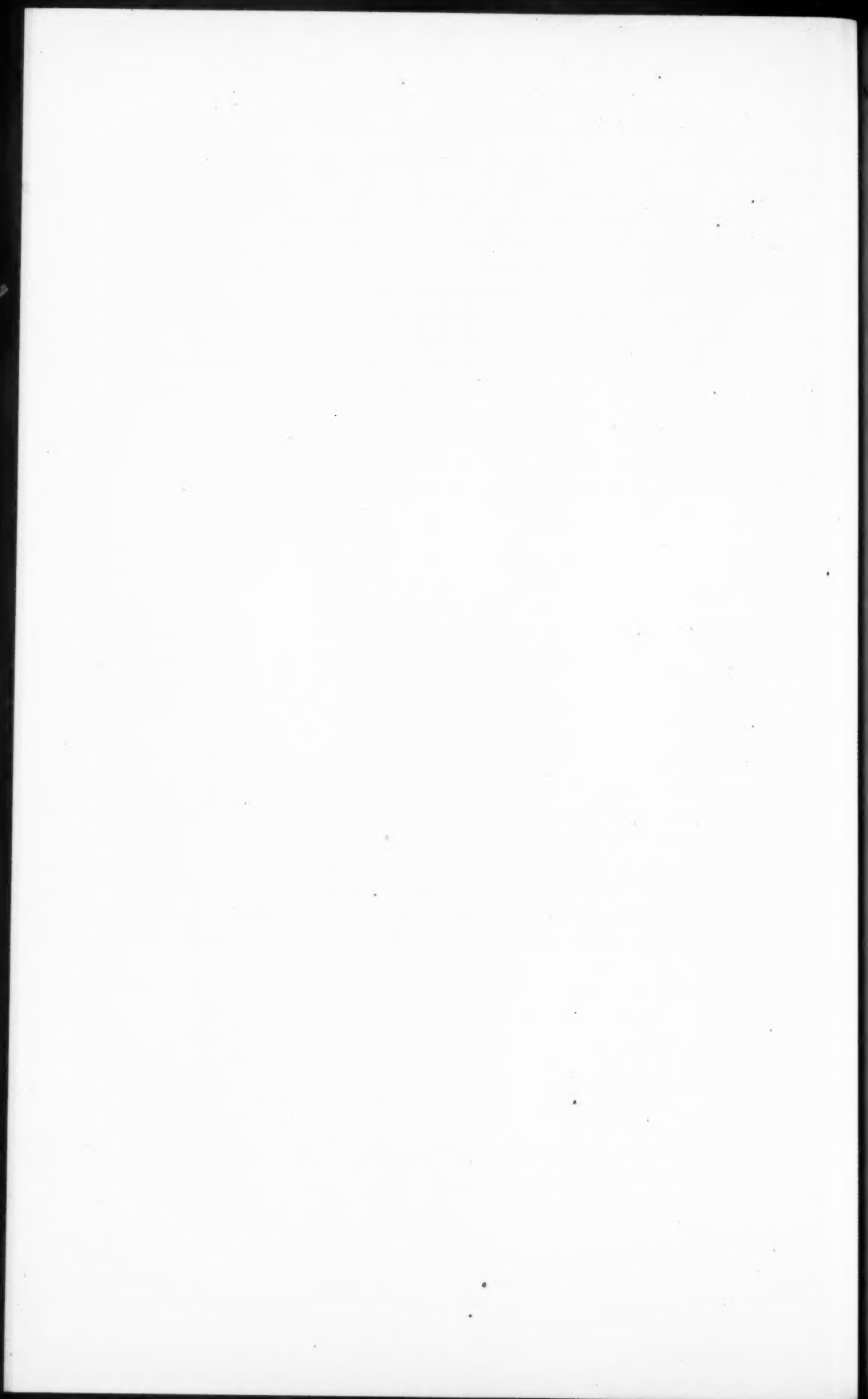
6. It is further suggested that the only true primary cardio-vascular contracted kidney is that of the senile arterio-sclerotic type.

So far as could be managed the sections on which the above reports were made were prepared according to a standard technique. Half the kidney removed in the post-mortem room was left in Kaiserling solution for from two to four days. Portions were then removed for cutting by the freezing method, and others transferred without washing to corrosive sublimate and bichromate mixture for mordanting prior to paraffin embedding. The blocks for the paraffin method were carried through graded alcohols and cleared in cedar-wood oil, this having been found to be much less damaging than xylol. The frozen sections were stained with Sudan III and Ehrlich's acid haematoxylin; paraffin sections were stained as a routine with Ehrlich's haematoxylin and eosin, eosin and methylene blue, Mallory's acid fuchsin and aniline blue orange G stain for connective tissue, and Weigert's resorcin fuchsin stain for elastin.

My thanks are due to Professor H. MacLean for giving access to the records of the St. Thomas's Hospital Medical Unit, and to the Medical Research Council, without whose assistance the work could not have been carried out.

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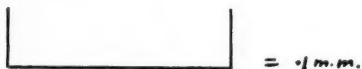
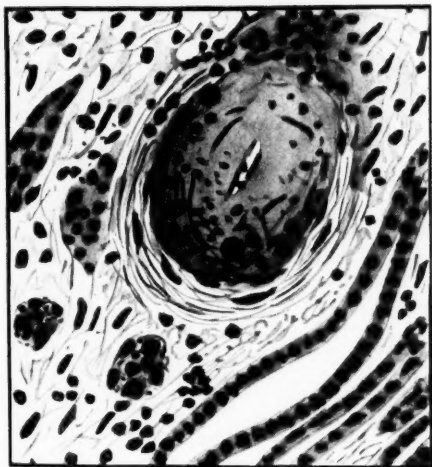


FIG. 1. Arterioles showing hyperplasia of the intima with fat change. From Case 44.



FIG. 2. Arteriole at point of departure from a larger vessel, showing fat change in the intima of the arteriole but not of the larger artery. Hyperplasia of intima of both.





FIG. 3. Glomerulus from Case 8, showing hyaline and fatty change of the tuft, with adhesions between tuft and capsule.

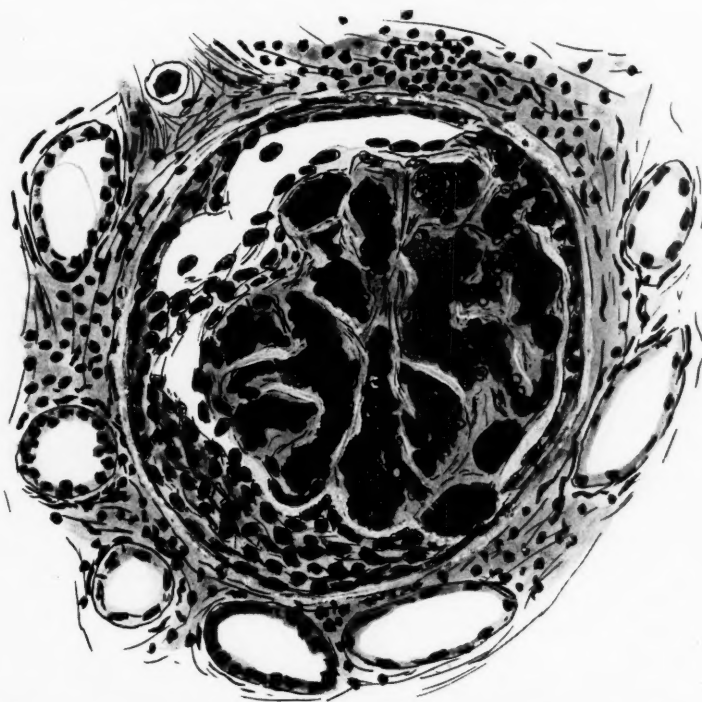


FIG. 4. Glomerulus from Case 44, showing proliferation of the endothelium of the capsule and tuft and haemorrhage into the latter.

THE RESPIRATORY EXCHANGE IN CRETINISM AND MONGOLIAN IDIOCY

By G. B. FLEMING

(From the Royal Hospital for Sick Children, Glasgow)

AT one time there was no sharp distinction drawn between Mongolian idiocy and cretinism. Though the chief points in the differential diagnosis are clearly given by many authorities (1, 10), even now the conditions are too frequently confused. In cretinism there is insufficiency of the internal secretion of the thyroid gland, and this is almost certainly the cause of the symptoms, while in Mongolian idiocy no cause has been discovered.

A striking feature of all diseases in which there is hypothyroidism is the low basal metabolism, and cretinism is no exception to this rule (3, 6). Though the metabolism of a considerable number of fairly old cretins has been examined, I can only find records of observations on one cretinoid infant (11). In all there is a marked lowering of the basal metabolism. In Talbot's case (the infant) there was a very low basal metabolism before treatment began, and after ten days of thyroid treatment this was greatly increased. Unfortunately there was much greater muscular activity in his second experiments, and consequently it is not possible to say how much the metabolism was raised by activity and how much by the drug. This is a difficulty which it is not easy to overcome in such cases. The untreated cretin is extremely lethargic, and as a rule it is easy to get a sufficiently long period of repose to examine the respiratory exchange; on the other hand, the cretin when treated with thyroid soon becomes extremely restless, and usually rather intractable. No doubt this is a sign of improvement, but it does not facilitate investigation of the basal metabolism. In two cases which I have had the opportunity to examine, numerous estimations of the basal metabolism were made, and it has been possible to get comparable conditions of muscular activity before and during treatment in both of them.

I do not know of any observations on the basal metabolism of Mongols, so in order further to differentiate them from cretins I thought it might be of interest to examine the respiratory exchange in some of these.

In both cretinism and Mongolism there is always marked under-development, and it is difficult to know whether to compare their metabolism to that of normal children of the same weight or the same age. The work of Benedict

and Talbot (2) provides us with data which enable us to make these comparisons. Their figures for the basal metabolism of normal children are used throughout this paper. The cretin owes a considerable proportion of its weight to myxoedematous tissue which is no doubt metabolically inactive. The Mongol, on the other hand, may be fairly well nourished, though the state of nutrition seems to show great individual variation, but there is always lack of muscular tone. In short, the Mongol is an undersized child, and the cretin, though also undersized, is loaded with a mass of metabolically inactive tissue which may amount to 10 or 20 per cent. of its total body-weight.

The Benedict-Talbot apparatus was used for the determination of the respiratory exchange. This is a closed circuit system and gives very accurate results. The technique followed was the same as that described by me in a previous paper (4). Alcohol control tests were frequently employed in order to check the accuracy of the apparatus. In each experiment a graphic record of the movements of the child was taken. As it is impracticable to reproduce these the degree of activity is indicated by numbers. An activity of I means practically no movement, the subject probably being asleep. Periods with slight movement are designated with the number II, and III, IV, V, and VI each apply to periods where there is increasing movement; with an activity of VI the subject is moving throughout the experiment and probably crying. The heat output was calculated from the respiratory quotient and the amount of oxygen used.

The Basal Metabolism in Cretinism.

J. D., male, aged 1 year 11 months.

Admitted 19.9.21. Normal labour, healthy at birth, weight 5.4 kilos. Breast-fed for 9/12. Throve well, was able at 9/12 to sit up, but never walked. Since that age the child had not developed. He had gradually become more and more lethargic, and although at one time he could say a few words he could not speak at the time of admission. The skin had always been dry and the feet and hands cold and blue.

On admission the child was seen to be a typical cretin with coarse bloated features, protruding tongue, harsh dry skin, hands and feet cold and blue. Apparently very fat. Large umbilical hernia. Fontanelle unduly open, no teeth, hoarse cry. Weight, 8.68 kilos; length, 68 cm.; sitting height, 46 cm.

Sugar tolerance. 4.10.21. 57 grm. glucose given fasting. No glycosuria.

X-ray of wrist showed ossification equal to that of a child of under 6 months.

On 23.10.21 put on thyroid, gr. $\frac{1}{2}$, three times a day. This was increased to gr. j twice daily on the 27th, and on Nov. 5 to gr. j thrice daily. Within a few days of the commencement of thyroid treatment loss of weight commenced and child became brighter. Thyroid treatment was continued till Nov. 19, and by this time there had been considerable loss of weight, 0.7 kilo, the skin had become warmer and less dry, and the child had become quite bright and active. Thyroid was stopped from Nov. 19 till Dec. 14. During this time the weight increased 0.9 kilo, the child became lethargic, the skin dry, and the extremities cold, though his general condition was not so markedly cretinoid as it was on admission. On Dec. 15 thyroid treatment was recommenced (gr. j twice daily); the weight immediately began to diminish, and the child soon became bright and

active once more. He was discharged from hospital on Dec. 27. On 2.2.22 he was readmitted to hospital. Thyroid treatment had been continued at his home. On admission he weighed 8.4 kilos, and he measured 71.5 cm. On Feb. 14 his sugar tolerance was tested. He was able to take 55 gm. glucose without glucose appearing in the urine.

On Feb. 22 he developed measles and was sent to Ruchill Fever Hospital.

A. D., female, aged 4 years 8 months.

Admitted to the Royal Hospital for Sick Children on 14.2.22. The child was said to have thrived till 1 year old. She was breast-fed for $1\frac{1}{2}$ years. She always had a poor appetite and was markedly constipated. She cut her first tooth at the age of 16 months. Her hands and feet are said always to have been cold and blue. She had never talked properly, but recently she had been able to say a few words. Eight months previously she was able to walk with assistance, but recently had not even been able to do this.

On admission the child was seen to be a typical cretin. The skin and hair were dry. She was apparently very fat. Weight, 11 kilos; length, 74.5 cm.; sitting height, 49 cm. The hands and feet were cold and puffy. The face was heavy looking. The eyebrows were fairly well developed. She was very lethargic. She had a hoarse cry. She could not stand. The heart appeared normal. There was some bronchitis. The abdomen was protruding and there was a slight umbilical hernia. The tongue was square and usually protruding. She had the full complement of teeth. The von Pirquet reaction was negative. The urine was normal.

Sugar tolerance test. 60 gm. of glucose were given fasting. There was no glycosuria.

Adrenalin test. 0.5 c.c. adrenalin 1/1000 injected intramuscularly. No reaction; no glycosuria.

X-ray of wrists showed ossification equal to that of a child of 1 year.

Thyroid treatment was commenced on 24.2.22, gr. j three times a day. This was increased to gr. ij twice daily on 3.3.22, but was reduced to the original dose on 15.3.22, and again increased to gr. ij twice daily on 19.3.22. This dose was continued till the child was discharged on 4.5.22.

During the course of treatment with thyroid the child lost 2 kilos in weight, and there was a vast improvement in the general and mental conditions. By May 4 the child was trying to talk. It was crawling about very actively, taking its food well, and the skin was soft and moist.

Table I gives the results of the respiratory exchange examinations in these two children. Both children were fed on ordinary mixed diet, and always drank about 150 c.c. of milk about forty minutes before the commencement of an experiment. In the first case, J. D., it will be seen that the metabolism was very low before thyroid was given. The total basal heat output per twenty-four hours was about what would be expected from an infant of about 6 months old. The administration of thyroid increased the metabolism by about 40 per cent. When thyroid was stopped there was a fall in the heat output, but this did not occur promptly. It took about three weeks for the effect of the thyroid treatment to wear off, and even then the metabolism did not fall to the original low level. On the resumption of thyroid treatment the metabolism immediately increased once more. The physical and mental condition of the child improved with the increase in the basal metabolism, and when treatment was interrupted there was a distinct retrogression in the general and mental condition.

In the second case, A. D., a similar low basal metabolism was found, and

this rose with thyroid treatment (Table I). Unfortunately it was extremely difficult to obtain periods of muscular repose, and on account of this on two occasions the child was given 5 gr. of chloral hydrate to induce sleep. In both these experiments a very low basal metabolism was found. Professor Pembrey suggested that this depression was probably due to the narcotic, and reference to the literature (7, 9) supports this view, though Tangl and Verzář (13) did not find a consistently lowered metabolism during narcosis produced by either morphia, urethane, or chloretone. Neither of these experiments, therefore, can be accepted as showing the true state of the metabolism. Eventually, by doing experiments at night, periods of repose were obtained without narcotics, and it will be seen that there was a marked rise in the metabolism compared to that found before treatment commenced—about 40 per cent.

It will be observed that though these children's ages were 2 and $4\frac{1}{2}$ years respectively, J. D.'s weight was about equal to the expected weight of a child of 10 months, and A. D.'s to that of a child of $1\frac{1}{4}$ years, but their heat output was only equal to that of children of about 6 months and 8 months respectively. So, whether the heat output be compared to that of a child of the same weight or the same age, in either case they both showed a greatly lowered metabolism.

After $3\frac{1}{2}$ weeks of treatment with thyroid J. D.'s metabolism had risen considerably, and was equal to that of a child of about 1 year old in spite of the fact that he had lost 0.5 kilo in weight. In A. D.'s case, after 5 weeks' treatment with thyroid, the metabolism had risen to that of a child of $1\frac{1}{2}$ years and she had lost 2 kilos in weight, which was by then only equal to that of a child of about 10 months old.

These results can be summarized briefly as follows:

J. D., aged 1-year 11 months.

Before treatment weight equal to that of a child of 10/12. Basal metabolism equal to that of a child of 6/12.

After $3\frac{1}{2}$ weeks' treatment, weight equal to that of a child of 8/12. Basal metabolism equal to that of a child of 12/12.

A. D., aged 4 years 8 months.

Before treatment weight equal to that of a child of 15/12. Basal metabolism equal to that of a child of 8/12.

After 5 weeks' treatment weight equal to that of a child of 10/12. Basal metabolism equal to that of a child of 18/12.

One of the striking features of both cases was that as soon as they were under the influence of thyroid, and had lost most of their myxoedematous tissue, they showed a metabolism which was higher than the metabolism to be expected from a normal child of the same weight (Fig. 1), indicating that all their active metabolic tissue required to make it function normally was a sufficiency of thyroid. Probably two factors at least caused the metabolism to be higher than would be expected from the weight. Though the children had lost most of their myxoedematous tissue it had not been completely replaced by fat, and consequently the active metabolic tissues were not 'diluted' to the normal

extent with tissue metabolically inert. This naturally would produce an apparent increase in metabolism when compared to body-weight, just as occurs in all conditions of under-nutrition in infants (4, 12). Secondly, these children were developing abnormally quickly, and an abnormally large amount of energy was being expended in the manufacture of new tissue. In other words, anabolism was going on at an increased rate.

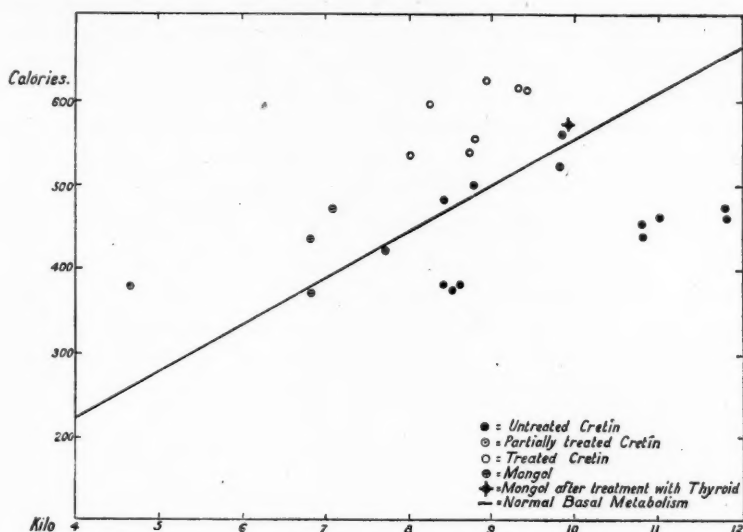


FIG. 1. The total basal metabolism per 24 hrs. referred to weight of cretins and Mongols. The continuous line represents the normal basal metabolism. (Talbot's cretin is included in this figure.)

The Basal Metabolism of Mongols.

T. S., male. A typical Mongol.

First respiratory exchange examination made when he was 10 months old; weight, 7.08 kilos; length, 65 cm. The next at the age of 14 months, and the subsequent ones between the ages of 2 years and 2 years 5 months.

The child was a patient in the Royal Hospital for Sick Children from March 21 till May 4, 1922. During this time the five last respiratory exchange examinations were made. The two first examinations were made when the child was attending the out-patient department.

Except for the mental deficiency, the typical facies, the protruding tongue, and the flaccid limbs, and the great under-development no abnormality was found. 24.3.22. Weight, 9.85 kilos; length, 78.5 cm.; sitting height, 48.5.

Sugar tolerance test. 46 gm. glucose given fasting—no glycosuria; three days later, 70 gm. glucose given fasting—glycosuria resulted.

Thyroid gr. j thrice daily was given from March 24 till May 4. There was no change in the mental or physical conditions of the child during this period.

J. M'C., male, aged 12 months.

Admitted to the Royal Hospital for Sick Children on 13.12.21, suffering from broncho-pneumonia.

On admission he was seen to be a typical Mongol, with slanting eyes, marked epicanthic folds, short bent little fingers, pointed protruding tongue, and great flaccidity of muscles. The heart seemed normal. There was a harsh respiratory murmur and râle at the bases of both lungs. Ears appeared normal. There was conjunctivitis and a considerable degree of nasal obstruction. Urine normal, von Pirquet reaction negative. He was poorly nourished; weight, 4.70 kilos; length, 64 cm.; sitting height, 42.5 cm.

The attack of pneumonia was mild, and the child made a good recovery. On Jan. 13 temperature (rectal) rose to 101° , and on Jan. 15 a typical measles rash developed. The child was sent to a fever hospital. The respiratory exchange experiments were done when the child was convalescent from pneumonia.

M. S., female, aged 1 year and 2 months.

Admitted to Royal Hospital for Sick Children 1.5.22. A typical Mongol. A very small well-nourished child, skin clear. Slight bronchitis. Heart appeared normal. No teeth, abdomen normal. Slight conjunctivitis and blepharitis. Much nasal obstruction. Throat red. Weight, 7.0 kilos; length, 68 cm.; sitting height, 45 cm.

J. M'D., female, aged 2 years 2 months.

Out-patient. A typical Mongol. Weight, 7.2 kilos; length, 74.5 cm. A fairly well-nourished child. Physical examination revealed no abnormality.

E. M'N., female, aged 20 weeks.

Out-patient. A typical Mongol. Weight, 4.0 kilos; length, 71. A well-nourished child. Physical examination negative.

E. R., female, aged 9 months.

Out-patient. A typical Mongol. Weight, 3.71 kilos; length, 55 cm. Fairly well nourished but very small. No abnormality found on physical examination.

Table II gives the results of the respiratory exchange experiments in these six Mongols.

In J. M'C. three observations were obtained, but in only one of them was the condition such that an estimate of the basal metabolism could be made, for in the second experiment the child was very restless, and in the third, though sufficiently quiet, he had a temperature of 101° and developed a measles rash the next day. Examinations of T. S. were made from the age of 10/12 to 27/12, and as a rule satisfactory conditions of repose were obtained. This child is of special interest as most of the observations were made when the age and weight were almost the same as those of the cretin J. D. Four examinations of M. S. were made, and in two of them satisfactory conditions were obtained. In the other three cases, in each of whom only a single observation was made, there was too great muscular activity to gauge the basal metabolism.

All these children show a metabolism which is lower than would be expected for children of the same age, but a metabolism approximately equal to or above that which would be expected for normal children of the same weight (Fig. 1). The height of their metabolism depended on the degree of development. Thus J. M'D., aged 2 years, whose weight was equal to that of a child of about 6/12, had the metabolism that one would expect from a

normal child of that weight, taking into consideration the fact that there was some activity during the experiment.

The very poorly-nourished subject (J. M'C.) had a heat output per kilo which was higher than normal, and this is in accord with what is found in all under-nourished children (4, 12). On the other hand, T. S. and M. S., who were well nourished, each had a basal heat output per kilo of body-weight which was almost normal (Fig. 1).

The examinations of J. M'C. are of interest, for on the last examination he had a temperature of 101° , the commencement of an attack of measles. On this day the metabolism was unduly high, showing that in Mongols fever causes a rise in the metabolism similar to that found in children of normal development (5).

The Effect of Thyroid Treatment on Mongolism.

Although no glandular extracts seem to affect Mongolism to any great extent Thursfield (14) is of opinion that thyroid does good in some cases. In view of this T. S. was given thyroid for five weeks and his basal metabolism determined at the end of this course of treatment. It will be seen from Table II that there is practically no rise in the metabolism, his total metabolism before treatment averaging 540 calories, and after treatment 565 calories per day. During treatment it was 603 calories per day, but on this occasion there was an activity of III which would be quite sufficient to account for the increased output on that day.

The Basal Metabolism of Cretins and Mongols Compared.

1. Both Mongols and cretins have a basal metabolism lower than that of normal children of the same age. This is largely due to the fact that in both cases there is retarded development.

2. Mongols have a basal metabolism as high as, or higher than, that of children of the same weight (Fig. 1). The under-nourished Mongol has a metabolism similar to that of any under-nourished child. On the other hand, the untreated cretin's metabolism is lower than that of a normal child of the same weight (Fig. 1). This is partly due to the fact that the cretin's body is to an abnormally great extent composed of tissue which is metabolically inert, but also it is probable that what active metabolic tissue there is works on a lower plane of activity than normal. The fact that after three weeks' treatment with thyroid J. D.'s metabolism rose 42 per cent., and after five weeks' treatment A. D.'s rose 38 per cent., is in favour of this hypothesis. The raised metabolism was probably in part due to the fact that growth was proceeding abnormally rapidly, but this heightened metabolism, when compared to body-weight, is a feature of all conditions where there is malnutrition, for in such cases there is a lessened amount of inactive metabolic tissue to 'dilute' the active tissue and consequently the body-weight: basal metabolism ratio appears high.

3. Whilst treatment with thyroid raised the metabolism in cretins it had no effect in a Mongol.

The Basal Metabolism as an Index of Nutrition.

The consideration of these experiments raised the question whether the rate of basal metabolism when compared to body-weight gives us an index of nutrition. There is no doubt that the weight to height ratio as a standard of nutrition gives no idea of relative proportions of metabolically active to metabolically inactive tissue, and in ideal states of nutrition there should be a definite relationship between these. The only method which can give us this information is the basal metabolism body-weight ratio. In ordinary cases of malnutrition in infants, growth in stature is not affected to nearly so great an extent as growth in weight, but in both cretinism and Mongolism there is always defective growth in stature, while the weight may be equal to the expected weight for the height. In short, they are always small, but they may or may not be undernourished.

Children suffering from these diseases, therefore, seem to afford us an opportunity of testing whether the basal metabolism gives us an index of nutrition. In cretins, however, a complication arises, for they are known to have an abnormally low basal metabolism due to lack of thyroid; but if this deficiency can be made good and their metabolism restored to the normal level, then they should fall into line with infants with a normal metabolism, and the height of the metabolism referred to weight should give us an index of their nutrition.

Benedict and Talbot (2) have demonstrated that up to about 12 kilos body-weight the basal metabolism of normally developed children is remarkably constant, about 55 calories per kilo per day. It has also been shown that children in varying degrees of emaciation have a heat output per kilo which increases with the degree of emaciation (4, 12). Both cretins and Mongols are undersized for their age and their weight to age ratio is no indication of the state of nutrition; but, if the weight-sitting height ratio (Pelidisi) according to von Pirquet's (8) formula¹ be determined, a better idea of the state of nutrition is obtained. Before treatment with thyroid A. D.'s Pelidisi was 98 and her heat output 41 calories per kilo for twenty-four hours; but at that time, owing to lack of thyroid, her metabolism was being carried on at an abnormally low rate. After five weeks' thyroid treatment her Pelidisi was 89, indicating a certain degree of malnutrition, whilst her metabolism was 70 calories per kilo per day. Before treatment J. D.'s Pelidisi was 98 and his heat output 44 calories per kilo per day. After four weeks' treatment with thyroid his Pelidisi had fallen to

¹ This formula is: $\text{Pelidisi} = \frac{\sqrt[3]{10g}}{Si}$, where g = weight in grm. and Si = sitting height.

100 represents a condition of normal nutrition. The lower the figure the greater the malnutrition.

92 and his heat output per kilo per day had risen to 67 calories. At first, in neither of these two cases did the ratio of heat output to body-weight give a true indication of the state of nutrition, because they were both suffering from a disturbance of metabolism due to lack of thyroid; later, however, when they had been treated with thyroid, the heat output per kilo of body-weight was about what would be expected from equally under-nourished children who had no disturbance of metabolism.

If in Mongolism there is no disturbance of metabolism, then, in spite of the fact that they are invariably undersized, we would expect to find that their basal metabolism follows the normal curve. That is to say, if they are under-nourished, they should have a heat output above that of a normal child of the same weight, and the same as that of any equally under-nourished child of the same weight, while if adequately nourished their heat output should be the same as that of a normal well-nourished child of the same weight. J. S. was well nourished, he had a Pelidisi of 96, and his heat output per kilo per day was almost exactly what would be expected of a normal child of that weight. On the other hand, J. M'C.'s Pelidisi was low (86), and his heat output was above normal for a normal child of the same weight but about what would be expected of any equally under-nourished child.

We thus see that the small Mongol with a normal Pelidisi had a normal metabolism, while the small cretin, which before treatment also had a normal Pelidisi, had a very low metabolism owing to the lack of thyroid, but after treatment, when its Pelidisi was low, the metabolism was above normal. From these considerations it is possible that in the absence of disease such as hypothyroidism or fever the basal metabolism rate gives an accurate method of gauging the state of nutrition, though until more rapid and easy methods are devised the basal metabolism rate cannot be of practical value for this purpose.

Summary.

1. The basal metabolism was found to be unduly low in the untreated cretin. Thyroid treatment raised the metabolism to about the normal level.
2. The basal metabolism was normal in six Mongols. Thyroid treatment had no effect on the basal metabolism of a Mongol.
3. Fever caused a rise in the metabolism of a Mongol.
4. The results of these respiratory exchange experiments in cretins and Mongols are used to test the suggestion that the basal metabolism rate referred to body-weight gives a reliable index of nutrition.

I have much pleasure in recording my thanks to Dr. Leonard Findlay and Professors Noel Paton and Cathcart for much valuable assistance and advice, and to the Medical Research Council, who defrayed the expenses of this investigation.

TABLE I.

Cretins.

Date.	Litre CO ₂ per hour.	Litre O ₂ per hour.	R. Q.	Total Cal. per 24 hours.	Weight kilo.	Length cm.	Activity.	Remarks.
J. D.								
18.10.21	2.65	3.27	0.81	378	8.60	70	II	1 year 11 months old
20.10.21	2.40	3.34	0.71	376	8.55	—	II	
21.10.21	2.43	3.36	0.72	379	8.4	—	I	
23.10.21	Thyroid gr. $\frac{1}{2}$ thrice daily							
26.10.21	2.79	3.33	0.84	388	8.6	—	II	Thyroid gr. j twice daily
31.10.21	3.39	4.18	0.81	482	8.4	70	II	
7.11.21	4.12	4.57	0.90	540	8.26	70.5	III	Thyroid gr. j thrice daily
10.11.21	4.35	5.11	0.85	596	8.26	—	II	
18.11.21	3.75	4.65	0.80	536	7.95	71	I	
19.11.21	Thyroid stopped							
5.12.21	4.46	5.46	0.81	630	8.44	—	I	
7.12.21	4.18	4.69	0.90	555	8.61	71	I	
13.12.21	3.84	4.15	0.91	492	8.75	—	I	
14.12.21	Thyroid gr. j twice daily							
23.12.21	3.66	4.65	0.79	534	8.7	71	I	
6.2.22	5.98	6.41	0.93	763	8.7	71.5	III	
7.2.22	4.77	4.62	1.03	559	8.76	—	II	
13.2.22	4.60	5.07	0.91	600	8.70	—	III	
A. D.								
16.2.22	3.07	4.04	0.76	460	11.0	74.5	I	4 years 8 months old
20.2.22	2.90	3.88	0.76	442	10.8	—	II	
21.2.22	2.98	3.97	0.75	451	10.8	—	II	
22.2.22	Thyroid gr. j thrice daily							
3.3.22	3.73	4.92	0.74	558	9.55	—	III	Thyroid gr. ij twice daily
7.3.22	3.87	5.08	0.76	579	—	—	IV	
9.3.22	6.88	7.76	0.88	912	9.14	—	V	
14.3.22	3.64	4.21	0.86	493	9.20	—	I	Chloral hydrate gr. v
17.3.22	3.04	3.63	0.80	418	9.0	76	I	" "
28.3.22	4.41	5.40	0.81	623	8.9	—	I	
11.4.22	5.08	5.04	1.0	610	9.36	—	I	
2.5.22	4.23	5.29	0.80	610	9.38	—	I	

TABLE II.

Mongols.

Date.	Litre CO ₂ per hour.	Litre O ₂ per hour.	R. Q.	Total Cal. per 24 hours.	Weight kilo.	Length c.m.	Activity.	Remarks.
T. S.								
17.12.20	3.52	3.99	0.88	469	7.08	65	I	10 months old
22.4.21	2.53	3.73	0.70	420	7.70	—	I	
25.1.22	4.65	5.50	0.84	640	10.05	77	IV	
23.3.22	3.72	4.54	0.81	524	9.81	78.5	I	
24.3.22	3.88	4.89	0.79	562	9.85	—	I	
26.3.22	Thyroid gr. j twice daily							
12.4.22	4.51	5.13	0.88	603	9.97	—	III	
1.5.22	4.06	4.87	0.83	565	9.9	78.7	I	
E. R.								
21.12.20	2.37	2.72	0.87	319	3.71	55	IV	9 months old
E. M.N.								
18.2.21	1.80	2.34	0.81	270	4.0	—	III	20 weeks old
J. M.D.								
28.10.21	3.65	3.90	0.93	464	7.2	74.5	IV	2 years 2 months old
J. M.C.								
6.1.22	2.88	3.24	0.89	381	4.64	64.5	I	12 months old
12.1.22	3.51	4.42	0.79	508	4.76	—	V	
14.1.22	3.41	3.93	0.89	463	4.76	65	II	
M. S.								
4.5.22	3.41	4.34	0.79	498	6.98	68	IV	1 year 2 months old
5.5.22	4.80	5.44	0.88	639	6.98	—	VI	
8.5.22	3.18	3.75	0.84	436	6.80	—	I	
9.5.22	2.76	3.15	0.88	370	6.80	—	I	

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ON RELAPSING PYREXIA IN LYMPHADENOMA, WITH AN ACCOUNT OF A CASE

BY ARTHUR J. HALL AND J. S. C. DOUGLAS

Introduction.

RELAPSING or periodic pyrexia occurring in cases of lymphadenomatous type has received much attention since the publication of Pel's (12) and more particularly of Ebstein's (3) cases in the early eighties. Altogether a considerable number of such cases have been recorded. MacNalty (8), in 1911, was able to collect thirty-two. Since then others have appeared, but the total of such records to-day is probably under fifty. Of these not more than a dozen can compare in duration with that of Ebstein; but, whether extending over shorter or longer periods, they all present certain features in common, and differ so markedly from what is seen in most other febrile diseases in temperate climates that their more close investigation seems desirable.

In trying to compare them with each other certain difficulties arise, due to:

(a) The great length of the ordinary charts, and the consequent difficulty of seeing the whole in a continuous line.

(b) The different thermometric scales used by British and continental observers.

(c) The varying ratio of width to height in the rulings of various types of charts.

(d) The different frequency of daily readings in different cases (four-hourly, eight-hourly, twelve-hourly).

To get over these difficulties and obtain comparable charts we have adopted a uniform standard chart, as follows:¹

1. The paper is ordinary sectional scale-paper, ruled in inches and divided into tenths.

2. The Fahrenheit scale is adopted throughout.

3. All records are 'morning and evening only'. (Most of the recorded cases

¹ The following statements of actual measurements refer to the original drawings from which the charts have been reproduced. It has not been found practicable to put the smaller sectional lines in the charts. Although individual charts vary in the size of their reproduction, they are all to the same scale, and made from drawings prepared as stated in the text.

are already of this kind. In those few cases where the records are at more frequent intervals, care has been taken to take those a.m. and p.m. records which indicate most closely the general excursions of the temperature during each period, so that the chart may follow the original as closely as possible. For our present purpose we are concerned with variations of days, or even weeks, rather than of hours.)

4. Each degree Fahrenheit occupies one inch vertically. Each day occupies one-fifth of an inch horizontally—i. e. one-tenth for the morning, and one-tenth for the evening record. The charts, as compared with the ordinary temperature charts, are thus compressed laterally and expanded vertically.

5. At the end of each calendar month, a vertical line is drawn, so that, although each date is not recorded, yet the temperature of any particular morning or evening in any month can be ascertained by simple measurement, in inches and tenths.

6. In order to obviate any visual deceptions produced by lines joining one another at varying angles according to their distance apart, all temperature-levels are shown by horizontal lines and all changes of level are joined by vertical lines. This arrangement, being so different from the 'dot and sloping line' with which we are familiar, gives the charts, at first sight, a strange appearance.

7. All horizontal space means actual length of time. One horizontal inch is five days, one month is six inches, more or less, according to the month. If there is a blank space, it means that for exactly so many days no record was made.

8. The standard charts here reproduced are accurate transcriptions of the originals (or carefully reduced to twelve-hourly records in cases where parts or the whole were four-hourly).

It is proposed in this paper to limit our remarks strictly to this question of the temperature peculiarity.

Most writers who have had the fortune to see one of these long cases, and the energy to record it, have taken the opportunity to give a short account of some or all of the previously recorded cases. Others have gone farther and published exceedingly valuable articles or even monographs on the subject. Amongst the latter the papers by F. Taylor (16), MacNalty (8), Batty Shaw (15), and Parkes Weber (18) contain much valuable information, with tabulated details and many original and interesting suggestions. These have been drawn freely upon in this paper, and we desire to acknowledge their help most fully. Particularly so in the case of MacNalty's thesis (8), published in 1911, which deals with the subject in a most thorough and masterly manner.

In considering these charts it is important to remember that they are not the product of one man's experience or one decade's work—they range in time over a period of over thirty years. Nor are they restricted to one area or to one country, or even to one continent. At rare intervals, in widely separated places, a case of this kind is recorded: sometimes it has been described as tuberculosis, at other times as lymphosarcoma, usually as lymphadenoma. Whatever may be the

true pathology the one common factor which has called attention to them is the relapsing pyrexia. This diversity of recorders both in time and place makes the similarity of the pyrexia in all cases the more convincing.

Account of a Case.

A case of this kind has recently come under our observation. The circumstances were such as to make the diagnosis during life very difficult. The history is as follows:

On May 10, 1920, a woman eighteen years of age was transferred from the Surgical to the Medical side of the Sheffield Royal Hospital. She had been sent in a few weeks previously on account of a supposed tubercular kidney. No evidence of this was found, but during the week preceding her transfer the temperature had risen steadily.

On admission she was obviously very ill. There was severe headache, delirium at times, a dry coated tongue, high fever, and slight tenderness over the abdomen. Except for a few rhonchi there were no abnormal physical signs in the chest. The liver and spleen were not enlarged. There was a well-marked Kernig's sign on both sides. Nothing definite was known at that time as to her previous history except that she was said to have been in a sanatorium for tuberculosis.

On May 20 her condition remained much the same. Lumbar puncture was performed. The fluid was clear, and under considerably increased pressure anti-meningococcic serum was given intrathecally and again on the 23rd. About this date the temperature began to come steadily down, remaining subnormal from the 27th. Her general condition improved greatly and she seemed to have made a remarkable recovery.

On June 2 she called attention to a small superficial skin abscess in the left axilla, which was opened and drained freely. She stated that she had been troubled with these previously, and the remains of others were seen in both axillae.

On June 14 she was sent up to the hospital's convalescent home in the country, where she continued to improve during the next week. Whilst she was still in hospital we heard that during her stay in a tuberculosis sanatorium she had suffered from previous attacks of pyrexia, but no details were known.

On June 21 she was sent back to hospital from the Annexe, her temperature having again gone up, with symptoms very similar to those in her previous attack. This fever was at first of hectic type, with extreme oscillations in the twenty-four hours. As it began to come down she got steadily worse. The spleen, which had not been palpable before, was enlarged and tender on June 24. Stupor and delirium with incontinence and rapid wasting followed, and she died, jaundiced, on July 13.

On June 23, two days after her return from the convalescent home, she complained of much pain in the left axilla and another large boil had to be opened. It discharged very freely for some days.

An autopsy was made on July 14, of which the following is the report:

The post-mortem examination was made the day after death.

Petechiae were present in skin of hypochondriac region, about left breast, and beneath left clavicle. Two deep punched out ulcers and many smaller ones over right gluteal region.

Sinuses, with overhanging thin margins, opening into larger cavities beneath the skin were present in the left axilla. These were not discharging. In right axilla was a small punctiform opening leading to an abscess which was burrowing beneath the skin.

General jaundice was noted in the skin.

On opening the skull, jaundice of the membranes was found, together with petechial haemorrhages on the inner aspect of the dura mater, whilst the pia-arachnoid showed a little oedema, particularly posteriorly. No meningitis was found.

The brain was normal save for pallor due to anaemia.

Lymphatic System.

No enlargement of glands was found save for a slight swelling of those at the bifurcation of the trachea, and in the post-thoracic region, which presented some carbon pigmentation. Lumbar glands slightly swollen.

An enlarged caseous gland and, near to it, a calcareous nodule were found in the mesentery.

A slightly enlarged gland was found in the left axilla, pink in colour, and suggestive of reaction to septic absorption. An enlarged pigmented gland was seen at root of right lung.

Spleen. Weighed 11 oz., being enlarged and congested. Small infarcts were present, and on section the organ showed much congestion and multiple abscesses, but no lymphadenomatous deposits were visible to the naked eye.

Respiratory Tract.

Larynx and Trachea. Nil.

Pleural Cavities. A little bile-stained fluid present on both sides. No adhesions found.

Right Lung. The colour was generally pale, but a little anthracosis was present. Two abscesses were found on the posterior aspect of the lower lobe about its middle, and another in the lower fringe of the middle lobe. Scattered purulent bronchitis was noted. The lung weighed 9 ozs.

Left Lung. A scar was present at the apex which was found microscopically to be due to tubercle. Several abscesses were present in the upper lobe where in contact posteriorly with the lower lobe. On section, oedema and traces of bronchitis were noted.

Circulatory System.

Pericardium. Normal save for some excess of fluid which was bile-stained.

Heart. Anterior aspect of right ventricle exhibited petechial haemorrhages. The heart-muscle was normal save for anaemia. Endocardium healthy, save that the valve cusps showed traces of bile-staining. The organ weighed 7 oz.

Vessels. No pathological change observed.

Alimentary System.

Tongue. Normal.

Pharynx. Normal.

Oesophagus. Normal.

Peritoneum. Presented slight oedema and scattered petechiae in right lumbar region of posterior abdominal wall.

Stomach. Distended with gas.

Intestines. Scattered petechiae on serous and mucous surfaces of small and large bowel. Bile-staining was noted.

Liver. Weighed 4 lb. 9 oz., being much enlarged. The surface was mottled,

being pale in places and in others reddish brown, and showed petechiae. On section the tissue was soft and bile-stained, and showed, mingled with the brownish-yellow colour of the liver substance, whitish spots and lines of a semi-opaque appearance.

Pancreas. Pale but normal.

Urinary Tract.

Right Kidney. Enlarged, weighing 6 oz. Anaemic. The capsule was adherent. On section the surface was pale and smooth, but cortex and medulla were well differentiated.

Left Kidney. Also enlarged, weighing 7 oz., presenting the same appearance as the right.

Ureters and Bladder. Normal.

Supra-renal Glands. Healthy.

Uterus and Appendages. Normal.

Breasts. Normal.

Bone Marrow. Red in colour.

Microscopical Examination.

The appearance of the organs, as above described, did not allow of a definite diagnosis, that of the spleen being compatible with a septic condition, especially as septic foci were found elsewhere in the body, whilst the semi-opaque material which permeated the liver suggested new tissue formation which, apart from other considerations, was consistent with infiltration by diffuse new growth, hypertrophic cirrhosis in an early stage, leukaemia, or lymphadenoma. Leukaemia was, of course, excluded by the absence of blood changes during life, and lymphadenoma, which had been expected, seemed doubtful in the absence of corresponding naked-eye glandular or splenic changes. The liver on section contained areas of tissue proliferation of lymphadenomatous type in which were embedded large cells, some of which were mono-, others bi-, and others again multi-nucleated, resembling the giant-cells found in that condition.

The presence of abscesses in the lung and spleen was confirmed microscopically, whilst pyogenic staphylococci were isolated from the pus in the axilla and from the spleen.

Lymphadenomatous tissue of type similar to that found in the liver was found scattered in small nodules throughout the spleen. Similar changes were seen in one of the mediastinal glands.

The kidney showed the presence of a little chronic nephritis. A few glomeruli were fibrosed, whilst there was a cellular increase in the intertubular connective tissue. Some of the tubules contained debris, and cloudy swelling was evident in the convoluted tubules.

Although at first the giant-cells were thought possibly to have a parasitic origin, yet no evidence in support of this idea could be found, and therefore pathologically the case seemed to be an example of the 'cryptic' type of lymphadenoma with the bulk of the change affecting liver and spleen, though lymph glands had not altogether escaped; the sepsis being the terminal phenomenon which accelerated death.

During the short terminal period of her illness in hospital no definite diagnosis was made. Even at autopsy the naked-eye conditions were somewhat indefinite, and it was not until a microscopic examination had been made that the diagnosis became tolerably certain. Some months later, thanks to the courtesy

of Dr. Rennie, Tuberculosis Officer to the City, we were shown the record of the patient's stay in the City Tuberculosis Sanatorium during the six months preceding her admission to hospital. This confirmed the pathological findings and showed that we had been dealing with a typical example of relapsing pyrexia in Hodgkin's disease (Fig. 7). The following are a few notes from Dr. Rennie's record:

'She began with what was called influenza in November 1918 (during the epidemic), and was laid up in bed for two weeks. Since then she has been unable to work regularly and has never menstruated.

'In September 1919 she attended at the tuberculosis dispensary, where she was classified as a case of "suspected tuberculosis". Sputa negative.

'In December 1919 she had her first recognized attack of pyrexia as shown in the chart.

'During five months' residence in the sanatorium she had five such attacks. Eventually, owing to the continued absence of pulmonary or other signs, and the recurrence of lumbar pain, renal tuberculosis was suspected and she was sent into hospital, as stated above.'

Periodicity.

It is obvious, in looking at the charts of Ebstein's (Fig. 4) and Melland's (Fig. 2) cases, that the waves of pyrexia succeed each other with remarkable regularity. But it is also evident that the intervals from one wave to its successor differ considerably in the two. In the former there are eight pyrexial peaks during seven calendar months, whilst in the latter there are twelve during a similar period. If these two hundred and ten days (seven months roughly) are divided equally, it would give a recurrence about every twenty-six days in the former, and every seventeen days in the latter. If one measures on the charts from the middle of each pyrexial wave to the middle of its successor, it will be found that on the whole this interval or 'span' in each case is repeated with considerable constancy. Each recurring wave is surprisingly punctual.

This method of measuring the curves and referring to them in terms of 'span' seems more useful than to refer to 'pyrexial and apyrexial periods' of so many days each. How misleading this latter method may be is well seen in Ebstein's (Fig. 4) and in Melland's case (Fig. 2). In the former, if by an 'apyrexial period' one means the number of days during which the temperature is normal or below normal, the duration of 'apyrexial periods' from December to March would be a steadily increasing one, whereas in reality the waves during that time are extraordinarily regular. Similar variability in the length of actual apyrexial, and, consequently, of pyrexial periods, is seen in Melland's case, and elsewhere in the charts.

The fact is that the waves may be perfectly regular in periodicity but at a slightly different level, the temperature dipping more or less in the different waves, so that the exact date at which it crosses the normal line of 98.4 is not so

important from a measuring point of view as the distance between the two successive waves. If the charts of the twenty-one cases recorded in the figures are measured according to 'pyrexial span' in this way, that is from the middle of one wave to the middle of the next, it is found that they vary considerably in different cases, from five or six days in MacNalty's Case II (Fig. 21), up to thirty-six days in his Case I (Fig. 26). But with the exception of these two cases and the long record of Hammer's (Fig. 1), which also has a very short span—the remaining 19 charts here reproduced have a 'span' between about fourteen and twenty-five days.

Thus in round numbers :

The span is less than ten days in 9 per cent.

between fifteen and twenty-five days in 86.5 per cent.

greater than „ „ „ in 4.5 per cent.

Another feature of interest which is shown by this measurement is that in each individual case the span remains constant within the limits of comparatively few days. There are exceptions (particularly in Hammer's case and in the one recorded in this paper) which will be referred to later. Another exception must be made in those cases where the chart is continued up to the time of death. This event is frequently preceded by a change in rhythm, which is so similar in different cases as to form an almost characteristic pre-lethal period (vide Ebstein (Fig. 4), Weber (Fig. 5), Pel I (Fig. 8) and III (Fig. 25), Whittington (Fig. 11), MacNalty IV (Fig. 15), Völekens (Fig. 10)).

These pre-lethal irregularities have been omitted from the following table on account of the difficulty in measuring them.

Table of Successive Pyrexial Spans (in Days).

	Days.	Days.	Days.	Days.	Days.	Days.	Days.	Days.	Days.	Days.	Days.	Days.
MacNalty II	7	5	5	6	7	7	5½	7				
Hammer	12	9	9	9	6	8	8	8	9	8	8	6
	7	7	8	8	8½	8½	7½	14	8	7	6	7½
	8	7½	11	9½	9							
Weber	13	13	15	16	14	17						
MacNalty III	(?) 20	14	14									
*Renvers	13	13	14	(?) 21	(?) 17	(?) 16						
Taylor, F. II	22	20	17	12	—	—	14	14	16	17		
Pel II	18	16	16	18								
Shaw, B.	18											
Melland	20	17	17	16	18	17	18	18	21	20	16	
Völekens	20	20	20	20	20							
Hall, de Havilland	20	20	20	20								
*Musser I	20	20	20									
*Musser II	21	16	22	15								
*Hofbauer	21	22										
Whittington	22	22										
Hauser	24	19	19	21	23	20						
MacNalty IV	19	21	23	22								
MacNalty V	23	27	18	18	23	23						
Ebstein	24	22	24	24	25	24	26	22				
MacNalty I	36	36										
Hall and Douglas	15	39	37	17	23							

From this table it is seen that in most cases the periodicity does not vary in any one case by more than five days, even during many months, as in Ebstein's and Melland's cases.

In some, such as Völckers', de Havilland Hall's, and Musser I, the punctuality of recurrence is remarkable. This punctuality is further emphasized by the following incident.

In MacNalty's Case I-only two successive waves are recorded on the chart published in his paper. These, however, show great similarity to each other, and as the span was much longer than that of any other record seen, the place on the chart where a third pyrexial wave should have come was measured and marked out on the standardized chart (Fig. 26).

Some days later when reading his account of the case the following passage was found: 'On leaving the hospital, the patient went to his own home at Ramsgate, when, for a space of three weeks, he appeared to recuperate rapidly: he then had a pyrexial attack which lasted from twelve to fifteen days, the temperature rising several times to 103° .' On looking at the marks previously made on the chart, it was found that the apyrexial period, as calculated by measurement, was exactly $4\frac{1}{2}$ inches (twenty-one days), and the estimated pyrexial period had proved accurate in every detail.

The two cases in which the variation in periodicity is very considerable are Hammer's (Fig. 1) and the case recorded in this paper (Fig. 7). In the former (Hammer's case), whilst most of the 'spans' range between seven and nine days, there is one of fourteen days intervening in a group of $8\frac{1}{2}$ to 7, i. e. just about double the length. It seems possible that this may be explained by one 'cycle' having for some reason been missed out at this point.

A similar explanation seems possible in the gross irregularities of our case. There are two long spans of thirty-nine and thirty-seven days, whilst the two following, if added together, form a span of forty, which is very nearly the same as the two previous long ones.

In four of the cases, Hofbauer's (Fig. 20), Renvers' (Fig. 18), and two of Musser's (Figs. 17 and 19), we have drawn what may be called 'conventional' charts. These authors do not publish the actual temperature charts in their papers, but merely state the dates at which the pyrexial periods began and ended, and this is recorded in the standard charts by the straight lines above and below the normal. They therefore merely record time and not height of temperature.

Some of these show marked regularity of 'span', but owing to the absence of a definite record it is difficult to measure them as accurately as the rest. In the case of Musser I (Fig. 17) the full record ends in January. After that the patient was only seen at rare intervals, and it is stated that on certain definite dates in the remaining months the temperature was raised or subnormal. These dates are indicated by solid lines, and it is found they correspond with what would have been the case had the recurrences been regular, as shown by the dotted line.

In addition to regularity in length of span there is on the whole a striking

similarity in the duration of successive periods of pyrexia, and in the height to which they attain. In other words, the 'form' of the wave in each individual case is fairly constant. The variation in height rarely exceeds two degrees, and is usually not more than one or one and a half. Thus, in Ebstein's long chart the peaks vary from 104.8° to 106.8° F. In Melland's they vary from 102° to 103° F. MacNalty's Case V (Fig. 16) shows the greatest irregularity in this respect.

These charts also show clearly the gradual stepping upwards and downwards of the pyrexial waves. As was noted by MacNalty, this steppage often precedes the point at which the temperature rises above the normal level, and is quite well seen whilst the temperature is still subnormal. It is seen in so many of the records that it is unnecessary to point out particularly good examples.

Lastly, the very low temperature records in the apyrexial periods are a feature of many of the charts.

The pyrexial records which correspond most nearly to these of lymphadenoma are found in that group of diseases which in most cases are known to be due to living organisms of various kinds—malaria, relapsing fever, rat-bite fever, trench fever, &c.

If we compare the 'span' in these various infections it is found that, as in the cases of lymphadenoma, they vary from each other considerably; thus malarial fever has the shortest span, two or three days; rat-bite fever, five days; trench fever, six or seven days; relapsing fever, fourteen days.

In lymphadenoma it has been shown that as a rule the 'span' is longer than the longest of these known organismal fevers. On the other hand, in two of the recorded cases (MacNalty II and Hammer) the span is as short as that of trench fever or relapsing fever, and nearly as short as that of rat-bite fever. Figs. 21, 22, and 23 show the standardized charts of MacNalty's Case II, of trench fever and of rat-bite fever cases respectively. The similarity of the charts in the three diseases is considerable. At least four of the lymphadenoma cases (Weber, MacNalty III, Renvers, and Taylor II) have spans no longer than those of relapsing fever. This difference in length of span does not therefore seem to be an insuperable argument against the view of its organismal origin; for, as was said above, there are considerable differences in span amongst those diseases known to be due to organisms.

Well-marked 'steppage' lasting over several days, such as is found in the slow long pyrexial waves of lymphadenoma, is obviously impossible in the more frequent and short waves of the fevers now under consideration. Even in these, however, it is frequently present to some extent (vide Fig. 24).

The very low subnormal temperature characteristic of the apyrexial periods of lymphadenoma is, however, quite eclipsed by those seen in relapsing fever. Rabagliati (13) records cases in which it reached depths (92.5° F.) lower than one would have thought compatible with life. As regards punctuality of recurrence referred to above, it is hardly necessary to emphasize how absolute this punctuality may be in the other periodic fevers, such as malaria, relapsing fever, &c. Finally, the remarkable feeling of well-being which is so frequently described in these

long cases of lymphadenoma has its counterpart in some of the other periodic fevers.

Thus in 'relapsing fever' reference is made to the difficulty of persuading patients to stay in hospital during the apyrexial period, because they feel quite well. In the article on relapsing or famine fever in Allbutt and Rolleston, Rabagliati (13) writes: 'Although I might succeed in keeping my patients in bed for a few days, yet they generally got up towards the close of the interval and before the *relapse*, which often therefore came upon them with all the force of the onset of a new disease.'

In the case which we record above, although it proved fatal a few weeks later, the girl seemed so well that she was able to go to a convalescent home and get about, even after a series of pyrexial attacks recurring at intervals during six months. This is possibly one of the reasons why more of these long charts cannot be obtained. The patients decline to stay in hospital during the long apyrexial periods.

It seems therefore that on the grounds of the pyrexia alone there is considerable evidence to suggest that this relapsing pyrexia may be due to some organismal infection, and the result of its life cycle.

It is obvious, however, that there are many difficulties in accepting this view. In many cases of lymphadenoma no such recurrent pyrexia is observed, but it is possible that in a less marked form it may be present at some period of the disease more frequently than is commonly thought. MacNalty alludes to this, and in looking over old records of these cases it is surprising to find how many of them show a definite tendency to recurrent pyrexia. Still, it is quite certain, as was pointed out by Gowers (21), that this recurrent pyrexia may be absent for long periods of the disease, or that it may be replaced by irregular pyrexia showing no periodicity. On the other hand, the periodic recurring pyrexia may continue through the whole course of the disease (Whittington's case, Fig. 11). Most commonly its advent means the beginning of the end, although that may not be for many months.

Up to the present no definite organism is generally recognized as the cause of lymphadenoma in any of its forms, but if the conclusions arrived at from a consideration of the pyrexia alone are sound, such an organism may yet be found, perhaps of protozoal type, and it is possible that, as in other cases of recurring fever, such causal organism may be detectable only at certain stages of the pyrexial cycle. In some of the cases careful investigations have been made, but it must be remembered that many of these cases were recorded at a time when much of the present-day knowledge of what have been termed 'protistal' diseases did not exist, and that investigation on such lines were lacking.

Cases of this type are not common, but further exhaustive investigations of the blood, or, if possible, of the juice from a lymphatic gland at a suitable period of the pyrexial cycle in such cases, seem desirable, and hold out the hope of a fruitful result.

Conclusions.

1. In certain cases of lymphadenoma there is a type of relapsing pyrexia which differs in certain respects from that seen in any other disease.

2. It resembles the pyrexia seen in that group of recurring fevers which includes malaria, relapsing fever, rat-bite fever, and some others, in:

(a) Regular periodicity;

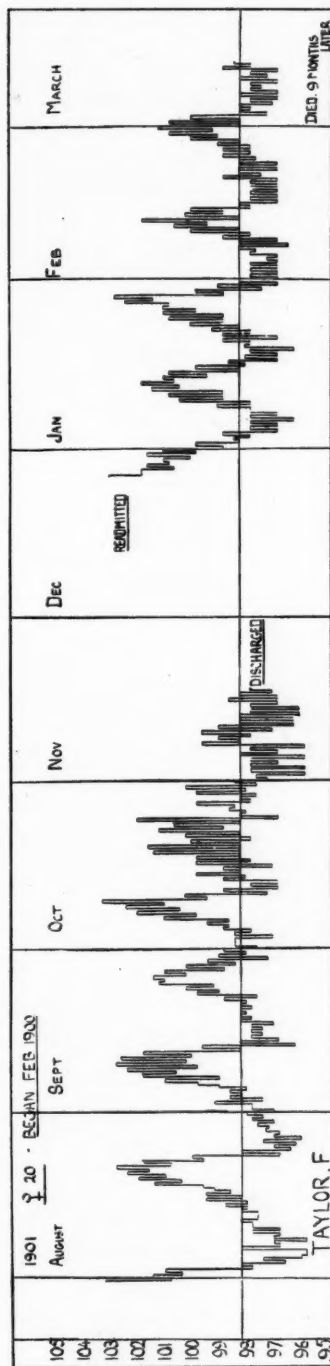
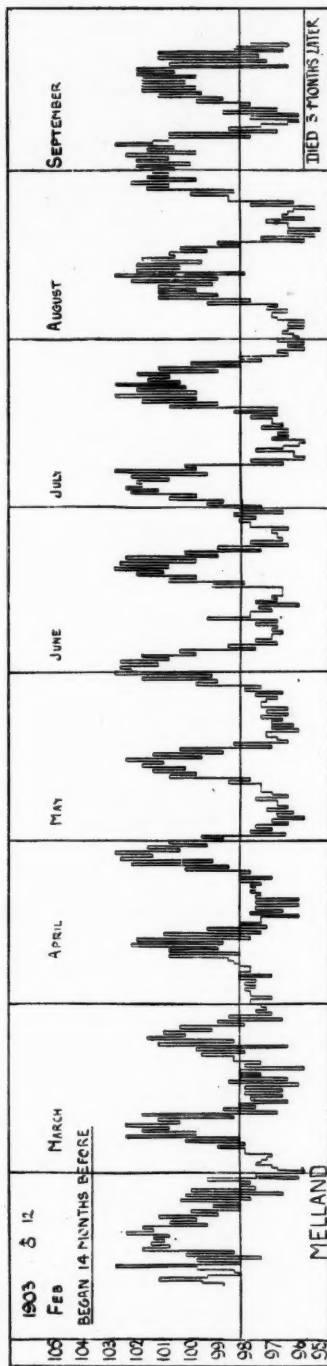
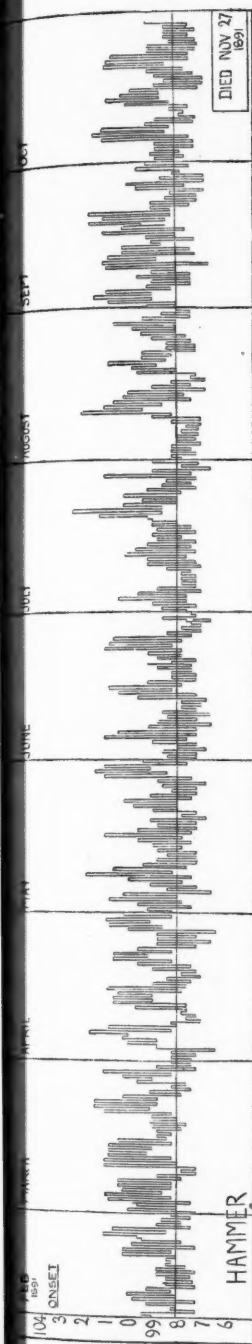
(b) Gradual ascent by steppage and sometimes similar gradual descent;

(c) Very low temperatures with apparently complete recovery in the apyrexial periods.

3. It differs from them in the greater length of span, which is usually from fifteen to twenty-five days, but may extend even to thirty-six days. It is usually fairly constant for each individual case.

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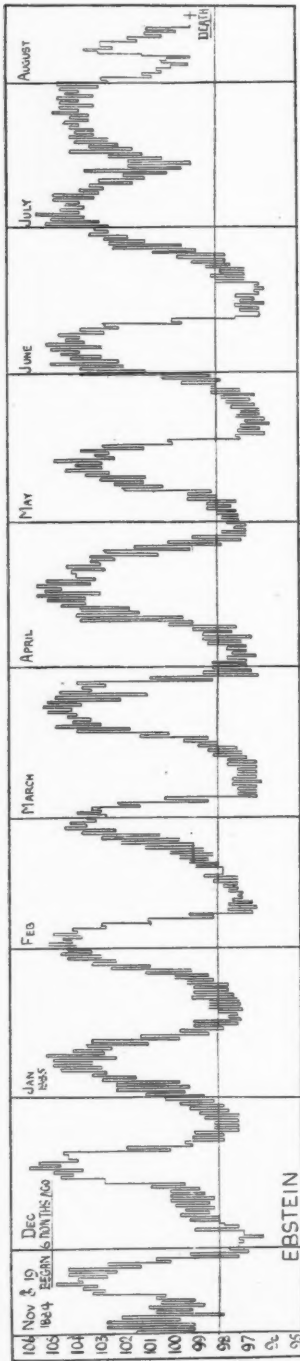


FIG. 4

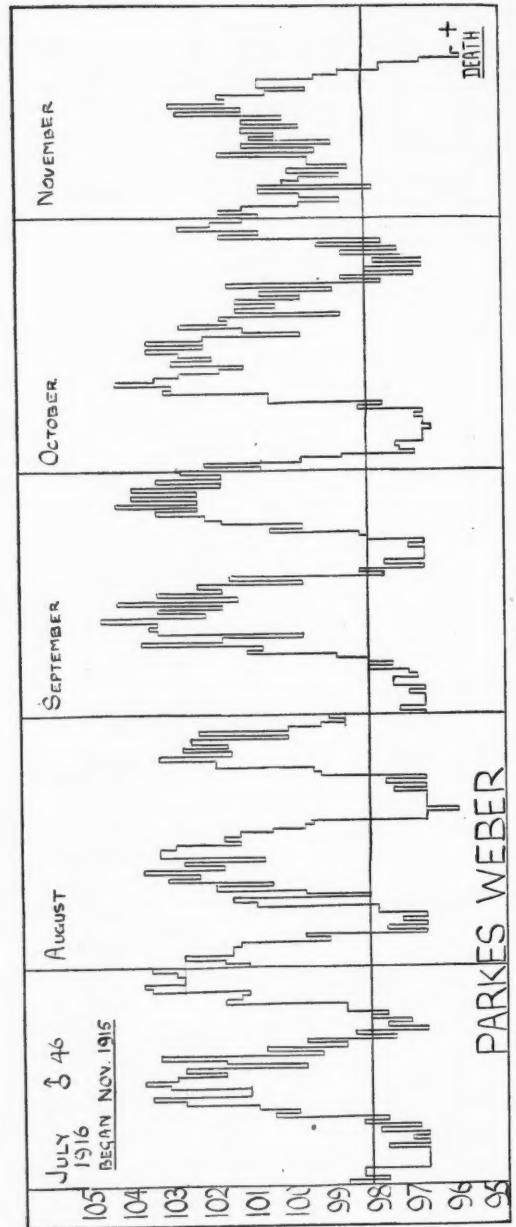


FIG. 5

FIG. 5

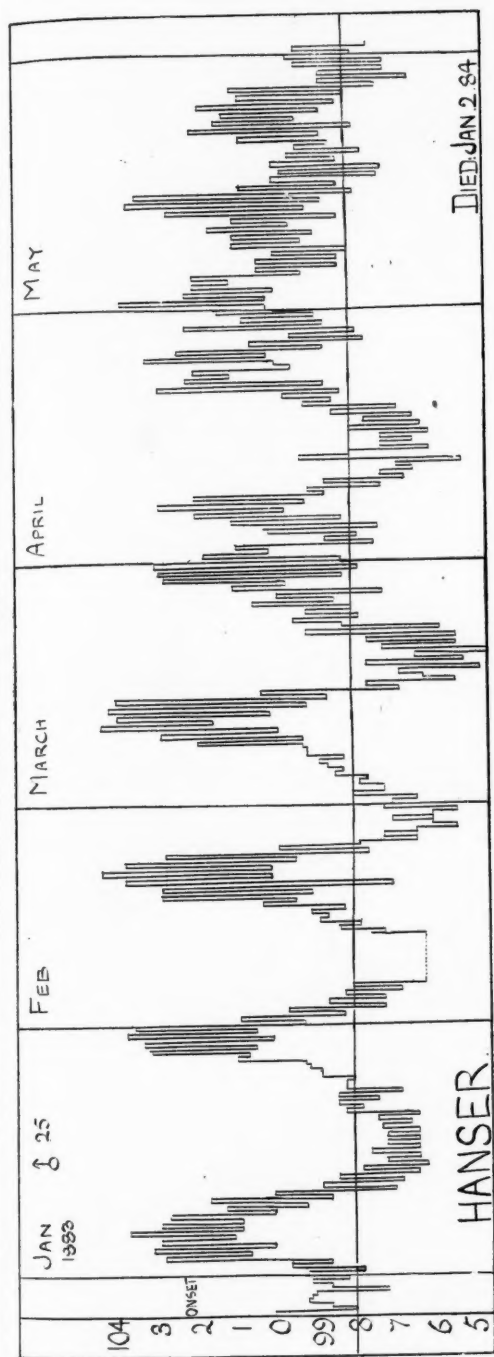


FIG. 6

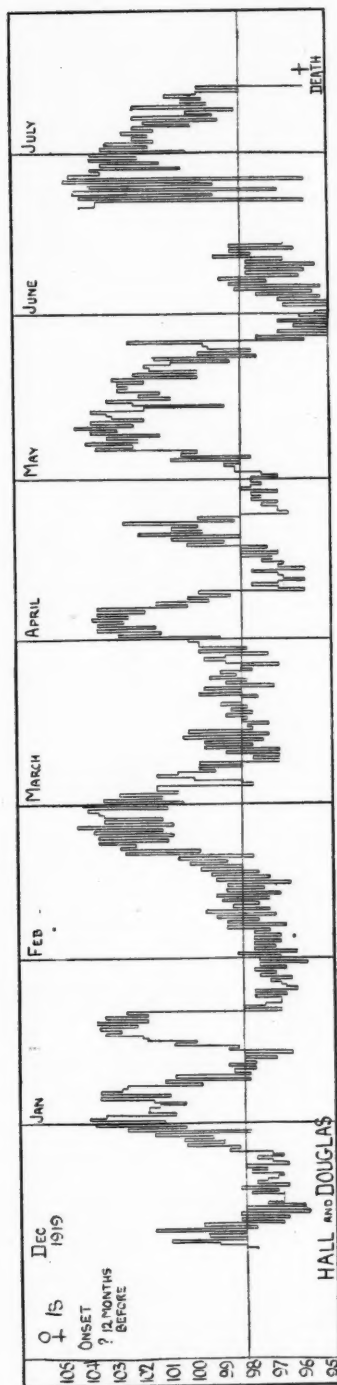


FIG. 7

IV

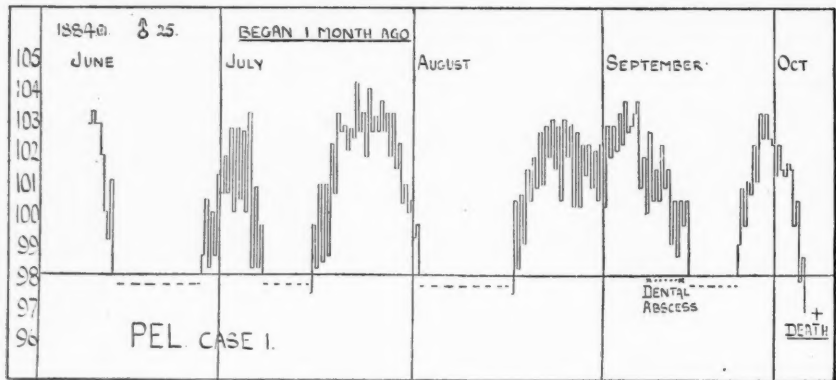


Fig. 8

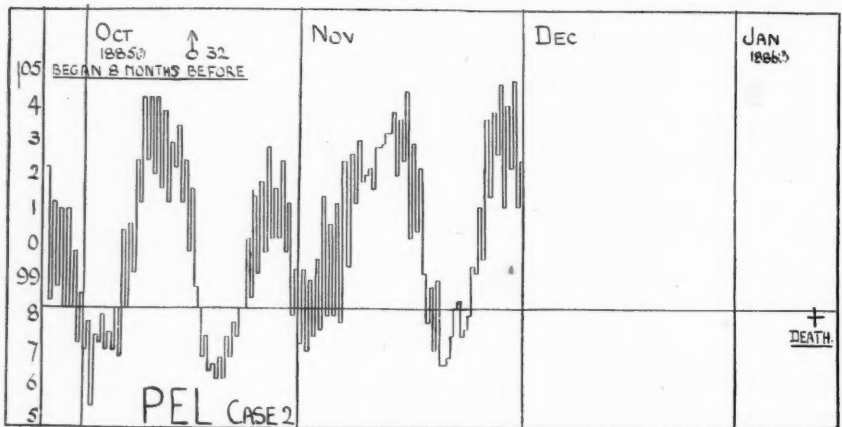


Fig. 9

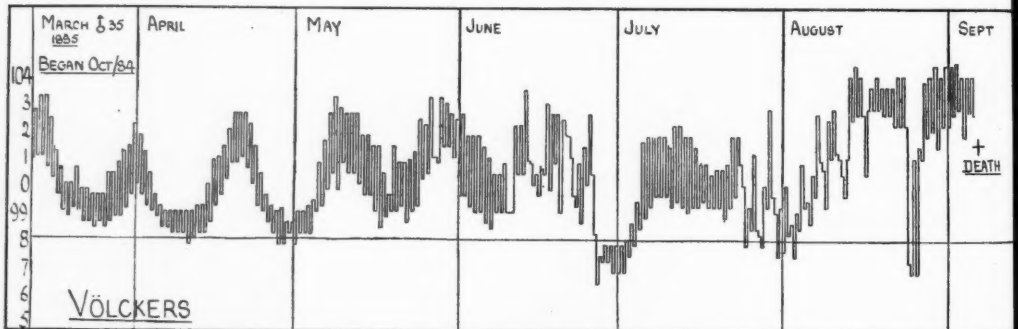


Fig. 10

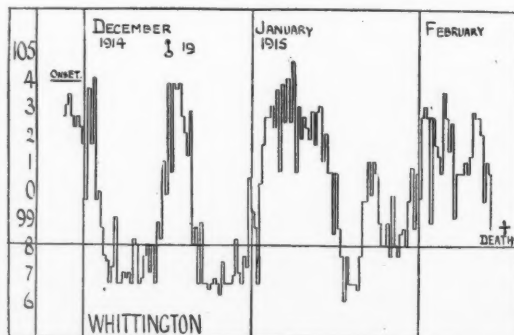


Fig. 11

FIG. 12

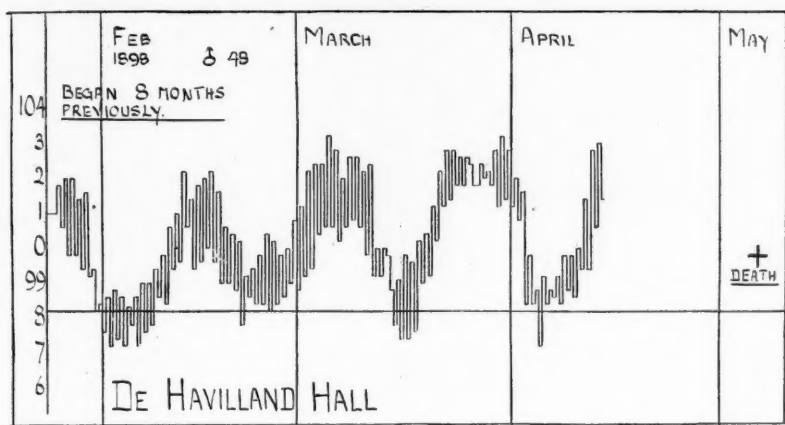


FIG. 13

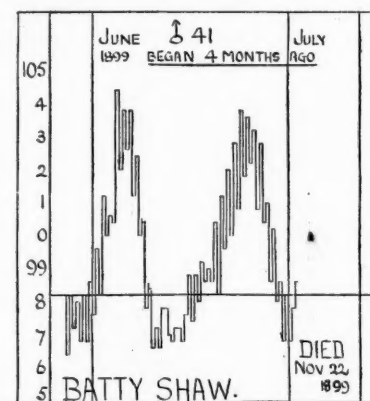


FIG. 14

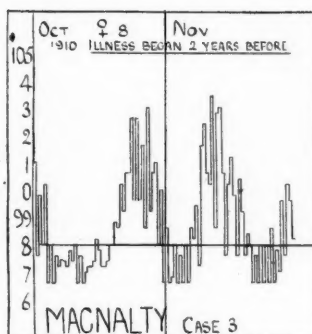


FIG. 15

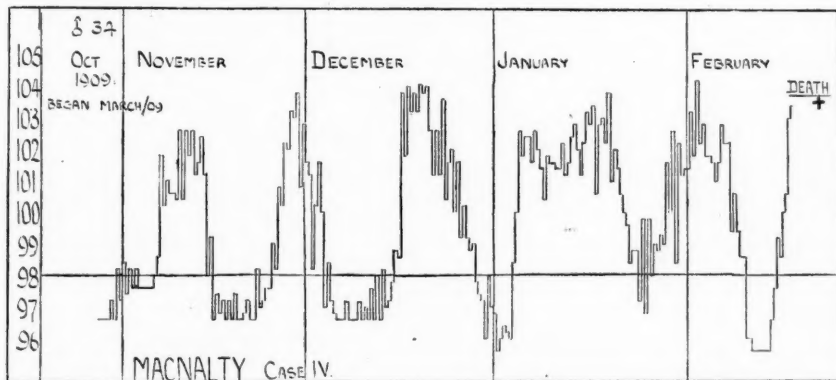
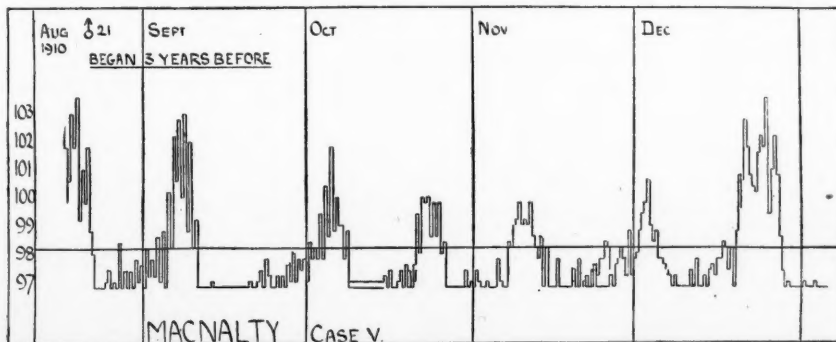


FIG. 16



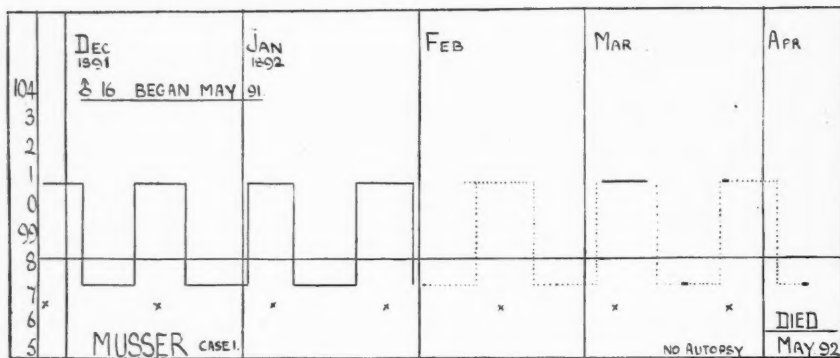


FIG. 17

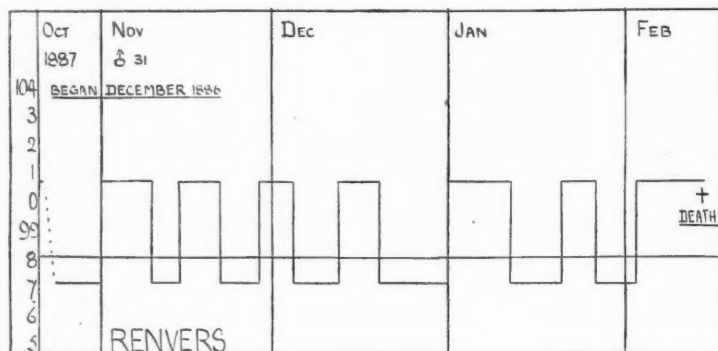


FIG. 18

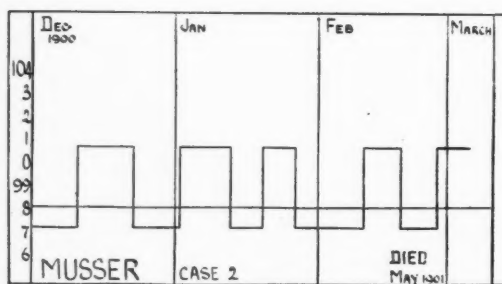


FIG. 19

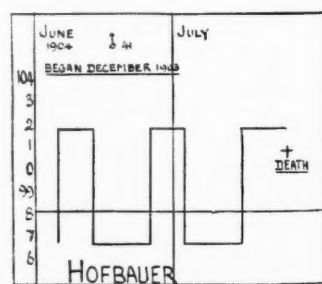


FIG. 20

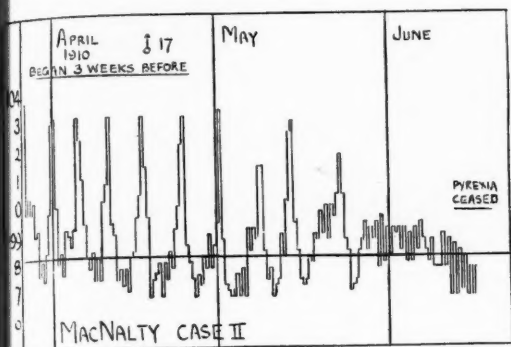


FIG. 21

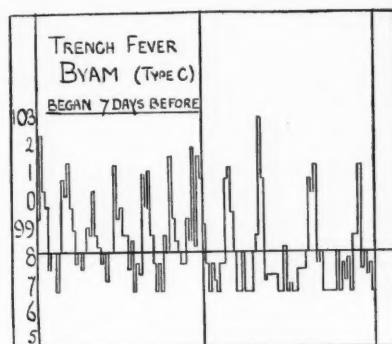


FIG. 22

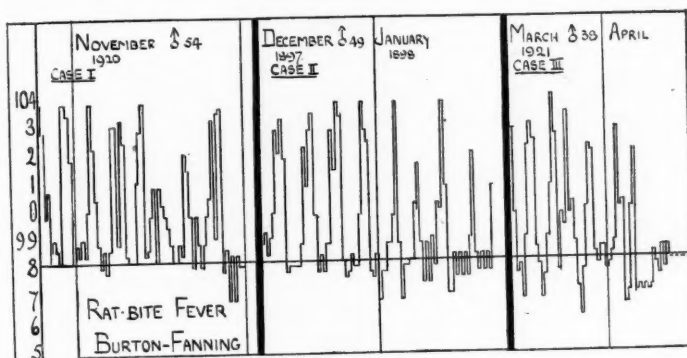


FIG. 23

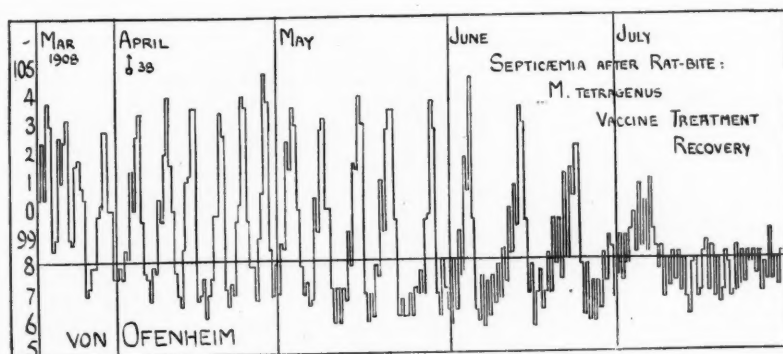


FIG. 24

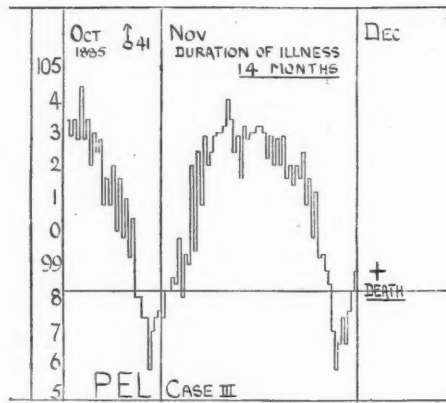


FIG. 25

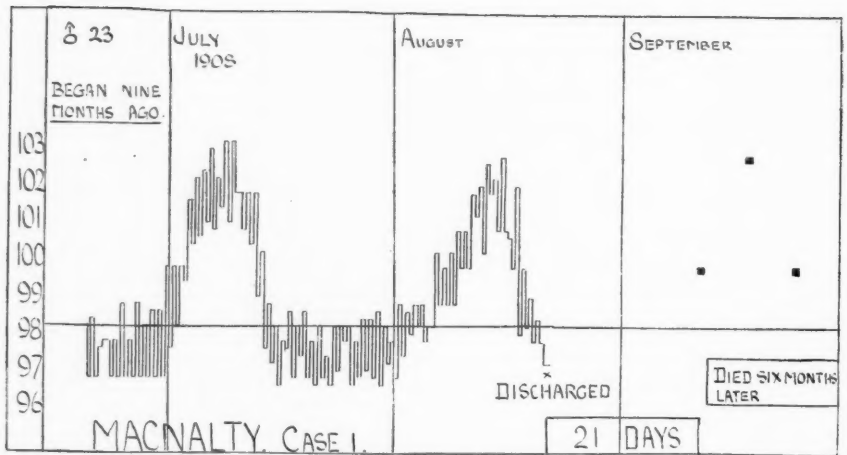


FIG. 26

ARTERIO-SCLEROSIS IN CHILDREN

By GEOFFREY EVANS

(From the Medical Unit, St. Bartholomew's Hospital)

With Plates 3-5

THE study of arterio-sclerosis in the adult led me to the conclusion that identical pathogenic factors might be responsible for different forms of arterial disease according to variations in the resilience of the tissues affected (1); that the difference between diffuse hyperplastic sclerosis and senile arterio-sclerosis, for instance, might be a question of varying physiological age response rather than a difference in the pathogenic agents involved. In other words, the younger the patient the more active was the type of tissue response to insult likely to be, and I expected to find the more active phases of arterio-sclerosis in children. This has been found to be the case in specimens to be described later which show endothelial cell proliferation in renal arterioles. Again, in elucidating the aetiology of arterio-sclerosis children provide a simpler material for study than do adults, because, by reason of their age, many of the aetiological factors that may be, or may have been, active in older subjects are *a priori* excluded. The difficulty, however, that occurs is the difficulty of obtaining suitable material, since the affection is not common in a well-developed form in children.

The four cases that form the subject of this communication are fairly complete in their clinical, chemico-pathological, and anatomico-pathological records. I had the opportunity of making the post-mortem examinations myself, and I am much indebted to Dr. H. Morley Fletcher, Dr. J. H. Drysdale, and Mr. Foster Moore for permission to see the patients during life and especially to publish the clinical records of their cases. Three of the cases have not been previously described; Case I was shown by Dr. Morley Fletcher at a meeting of the Children's Section of the Royal Society of Medicine (2). The correlation of clinical and chemico-pathological (renal efficiency tests) observations with the post-mortem findings is of great interest, and it is on this account that the clinical details of Case I are repeated in this report. The first three cases belong to the type of chronic nephritis in childhood commonly named renal infantilism. The fourth case is different in some respects both clinically and pathologically, but in the similarity of the renal and cardio-vascular affection it is sufficient for the present purpose to place it in the same group with the other three. Similar cases

to those described here have been reported by several authors (3), (4), (5), (6), (7), and (8), who give references to other cases in the literature. The outstanding feature of the present series of cases was the marked degree of cardiac hypertrophy and abnormally raised blood-pressure.

Clinical and Pathological Records.

Case I. Female, aged 14, admitted to hospital under the care of Dr. Morley Fletcher, three months before death, complaining of weakness and headache.

H. P. C. Onset insidious and perhaps congenital; she was 'small and delicate all her life', 'very weak since birth', liable to frontal headaches and nocturnal enuresis for years past. For a few weeks before admission there was complaint of pain and deafness in the right ear; no aural discharge. No history of gastro-intestinal disorder.

P. H. Scarlet fever two years previously, an illness which did not seem to have a permanent influence on her already weak state of health.

F. H. Nothing indicative of syphilis.

P. C. In physique a 'renal dwarf'. A very small body, pallid and wasted; no sign of puberty. Weight 2 st. 7 lb. No enlargement of the liver or spleen; no sign of syphilis; blood W. R. negative. No oedema. There was marked cardiac hypertrophy; the radial artery was small and wiry; marked thickening of the carotid arteries and very marked arterial pulsation in them. The blood-pressure varied between 250 mm. Hg systolic, 170 mm. Hg diastolic, and 175 mm. Hg systolic, 135 mm. Hg diastolic. Mr. Foster Moore's note on the optic disks was as follows: 'Disks obscured by oedema, themselves are somewhat pale. Arteries and veins are diminished in size. The veins are cut into where the arteries cross them. Haemorrhages are scarce and small; in each eye a particularly well-marked star figure. In a few places well-marked sclerosis of the choroidal vessels is visible. From the pallor and absence of marked swelling of the disk, the small retinal vessels, the absence of haemorrhages, and the pigmentary changes I should judge that retinal changes have been present for some time.'

Urine. Pale, slightly turbid, no deposit, acid; sp. g. 1010, 0.3 per cent. protein, of which a considerable proportion was globulin. The centrifugalized deposit contained numerous R. B. C., less numerous W. B. C., a few granular casts, no crystals. Blood urea 90 mg. per cent., later 168 mg. per cent. MacLean's concentration test: Urine before the test contained 1 per cent. urea; in the first hour after giving 5 gm. of urea the specimen contained 0.9 per cent.; the specimen passed at the end of the second hour also contained 0.9 per cent. Urinary diastase 10 units. Blood-sugar 0.1 gm. per cent. Temperature normal during the three months in hospital; pulse-rate generally about 110. In the last few days there was ingravescent coma, and death occurred on June 3, 1920, in a convulsion. The outstanding clinical features were the retarded development, poor physique, and wasting, good mentality (7th standard at school), the marked renal insufficiency, and the great degree of the cardio-vascular affection.

Post-mortem, 4.6.20. *Uraemia.* Chronic nephritis; atrophy of the left kidney; right, pale and granular. Hypertrophy of left ventricle. Arterio-sclerosis affecting the aorta, coronary arteries, and carotid. *Heart*, 7½ oz.; marked hypertrophy left ventricle, muscle pale, good firm texture. *Vessels*: marked sclerosis of the arch and descending aorta, irregular oval and circular plaques of intimal thickening, some pale and semi-translucent, others yellow (fatty); in descending aorta two areas of fibrosis. No ulceration. Common iliaes normal, except for medial hypertrophy, which was marked in all arteries, including the aorta. Mesenteric vessels normal. Right carotid showed marked longitudinal streaks of fatty intimal degeneration. Left carotid not opened. Early nodular

sclerosis at the beginning of both coronary arteries. Marked nodular sclerosis in middle cerebral arteries and in their branches; circle of Willis similarly affected to a less extent. Right radial artery appeared normal. *Pituitary, thyroid, and thymus* glands normal. *Suprarenals* much hypertrophied. *Kidneys*: right $1\frac{1}{2}$ oz., adherent to perirenal tissues, which were not themselves thickened or matted. Small vessels in abnormal number run in from perirenal tissues through capsule to cortex of kidney. Organ shrunken, not deformed, surface pale and mottled, intensely granular, the granulations uneven and coarse. Cut with resistance. Pelvis enlarged and inflamed; no peri-pelvic fat. Cortex atrophied to a thin line and normal kidney structure lost; large areas of pale fibrosis give mottled appearance to cut surface in which pyramids appeared dark by contrast. Capsule thickened and stripped with difficulty, tearing the renal substance. Left, $\frac{1}{2}$ oz. Similar, but the changes were of extreme degree. In both the renal vessels stood out on section like little quills. C. S. F. urea *post mortem* 660 mg. per cent. (Dr. Canti). *Ureters* large, somewhat dilated. Bladder-wall somewhat hypertrophied. *Urethra* and *ureteric* openings normal. *Uterus* infantile.

Histology.¹ Advanced chronic nephritis. The most prominent changes were in the interstitial tissues. There was great increase in the fibrous tissue, diffuse small-cell infiltration and extreme obliterative endarteritis affecting the vasa recta to such an extent as almost to obliterate the lumen of many vessels; the parent arteries of these vessels were similarly affected to a less extent. There was no fatty degeneration in the majority of these arteries. The terminal arterioles, the vasa afferentia, were much reduced in number; typical examples of type seen in diffuse hyperplastic sclerosis in adults were present. There was extreme atrophy of the parenchyma. The glomeruli were reduced in number, those that remained were mostly reduced to fibrous nodules; some that were less completely destroyed showed endoglomerulitis with proliferation of the epithelial cells of Bowman's capsule and adhesion of the parietal and visceral layers. The tubules in some areas were conspicuously absent. Those that had escaped destruction were atrophied and dilated, while there were also sparse areas of tubules that had undergone a compensatory hypertrophy; some of the hypertrophied tubules had undergone fatty degeneration.

The prominence of the fibrosis and small-cell infiltration in the histological picture has led to the opinion that the interstitial tissues bear the brunt of the insult in this affection; hence the condition is generally called 'chronic *interstitial* nephritis'. The parenchyma, however, is equally or more severely damaged, and as a result is largely destroyed. Since all the tissues of the kidney are affected the lesion is better termed 'chronic nephritis'. The state of the arteries in other organs is given in tabular form on p. 39 for comparison with the other cases.

Case II. Male, aged 14, admitted to hospital under the care of Dr. Drysdale three months before death complaining of defective vision.

H. P. C. Onset insidious. The condition was first discovered seven years before death, when the patient had an epileptiform convulsion in hospital on the day following an operation. The child had been admitted on account of genu valgum and Macewen's osteotomy had been performed. The following notes were made after the transfer of the patient to Dr. Morley Fletcher's ward: Weight, 2 st. $12\frac{1}{2}$ lb. Height, 3 ft. $2\frac{1}{4}$ in. Systolic blood-pressure 195-170 mm. Hg. Urine, sp. g. 1023 or less. Protein (which gave all the reactions of globulin) 0.001 per cent. Epithelial casts present. 30 oz. passed in twenty-four hours.

¹ Dr. J. F. Gaskell's gelatin method was employed for the preparation of specimens for microscopical examination (9).

Renal efficiency tests (Dr. Trevan): 'Excretion of sodium chloride indicates that tubules are probably in good working order. This was confirmed by normal excretion of potassium iodide; but there was a great rise in the water excretion, indicating that his cardio-vascular apparatus and glomeruli are disorganized. Excretion of lactose normal, and therefore glomeruli are not much damaged.' Marked cardiac hypertrophy was present at this date. The optic disks were passed as normal.

After discharge from hospital the boy remained in his usual health for six years, when his eyesight began to fail. At about the same time he began to suffer from occipital headaches, but throughout these years there was no history of oedema, frequency of micturition, haematuria, pain in the back, or other digestive disturbance than an occasional pain in the stomach half an hour after his meals.

F. H. Patient was seventh of nine children, having four sisters and five brothers all alive and well. His mother had four miscarriages before his birth. Mother alive and well. Father died of pneumonia.

P. H. Normal labour; breast-fed to 11 months, then potatoes and gravy. Walked and talked at usual age. Measles, aged 4; broncho-pneumonia, aged 5; T. B. gland in neck opened, aged 8; bronchitis every winter. No history of chorea, rheumatism, scarlet fever, or fits.

P. C. Under-developed, mouth-breather, somewhat pigeon-chested, Harrison's sulcus present. Rickety bowing of the tibiae; X-ray appearances of bones of lower limbs were those of rickets. No signs of syphilis. Blood W. R. negative (as also seven years previously). No oedema. Marked cardiac hypertrophy; the radial artery was thickened; there was such marked visible and palpable pulsation in the 2nd right intercostal space that aneurysm of the aorta was suspected. X-ray examination showed a dilated aorta. B. P. 260 mm. Hg systolic, 200 mm. Hg diastolic. Optic disks: Rt. 6/18. Oedema of disk. Well-defined area of exudate to outer side of disk; star-shaped figure round the macula; patches of pigment in periphery of eye. Lt. 6/18. Haemorrhages grouped about the vessels all over the retina; black spots at macula and many at periphery; star-shaped figure round yellow spot and much exudate of like character (Mr. Foster Moore). Urine sp. g. 1012, acid, albumin 0.025 per cent.; no casts or cells in a centrifugalized deposit. Later, a few W. B. C., granular and epithelial casts were found in the centrifugalized deposit. Average excretion of urine 45 oz. Blood urea 67 mg. per cent. (Dr. G. Graham). Potassium iodide excretion in first twelve hours 26 per cent. of dose given—normal 45 per cent. (Dr. Linder).

Three months later the patient was readmitted unconscious. He had complained of sickness and headache for the past few days. On the evening before admission he had a convulsion and became unconscious. He died soon after admission, obviously a case of cerebral haemorrhage without localizing signs.

Post-mortem, 16.8.20. Cerebral haemorrhage, left capsular, rupture into ventricles; left ventricle, hypertrophy, arterio-sclerosis; chronic nephritis.

Heart. 12 oz., marked hypertrophy left ventricle; muscle, endocardium, and pericardium normal.

Vessels. The aorta showed only slight evidence of sclerosis. In an adult it would have passed as normal in this respect; its media was much thickened, as was that of the other vessels. In the carotids were long narrow streaks of fatty sclerosis; the vertebral and basilar arteries normal; small patches of nodular sclerosis in the middle and posterior cerebral arteries.

Kidneys. Left, 5 oz., adherent to perirenal tissues by numerous small adhesions, surface coarsely granular, mottled white and bluish red; capsule adherent and split on stripping, tearing cortex on complete removal. Organ firm on section; cortex narrowed, normal structure blurred; colour of cut surface mottled grey and purplish red with scattered pin-point haemorrhages; the pyramids somewhat dark in contrast to cortex. Pelvis increased in size; no pyelitis; increase in peri-pelvic fat. Rt., 1 oz., shrunken, globular shape. On section there

appeared to be a congenital reduction in substance, there being only two well-formed pyramids. On the surface an indefinite smoother (? scarred) area; in other respects this organ resembled the left. Both renal arteries showed arterio-sclerosis, and in the right, near its division into branches, there was a calcified oblong plaque. The *ureters* and *urinary bladder* were normal. Several enlarged caseous lymphatic glands in the mesentery. Adhesions present at base of left lung binding visceral pleura to diaphragm. Petechiae were present on the pleural surfaces of the lungs, under the peritoneum, and in the skin of the lower limbs.

Histology. Chronic nephritis showing a remarkable degree of recovery. The microscopical appearance was unusual. The great degree of tubule regeneration dominated the picture; the tubule epithelium stained well; some desquamation of cells, but the lumina, which were somewhat dilated, did not contain casts. The glomeruli showed regeneration almost uniformly. On careful examination many were found to show slight proliferation of the epithelial cells of Bowman's capsule, and there was a sparsely scattered focal lesion in the tufts resembling that found in focal embolic nephritis. There was an absence of hyaline degeneration and fibrosis of the tufts. The amount of interstitial change was relatively small; slight round-cell infiltration around some of the glomeruli and a few polynuclear cells. The typical lesion of diffuse hyperplastic sclerosis was present, and Plate 3 shows two arterioles in active phase of this lesion. The section suggested the regenerative stage of a chronic nephritis in the tubular and glomerular hyperplasia; while the relatively small degree of arterial change suggested that this tissue also had made good recovery.

Case III. Male, aged 9, admitted to hospital under the care of Dr. Drysdale six months before death, complaining of headaches and vomiting. His first admission to hospital was six months previously, when he was brought up by his mother on account of nocturnal enuresis. There was some evidence that his illness dated from an attack of scarlet fever three years before. Definite symptoms developed a year before death, namely, headache in the early morning, disappearing after breakfast, and occasional attacks of vomiting in the morning or late afternoon. Apart from the history of scarlet fever there was no fact of importance in the past or family history. There was no history of oedema, haematuria, gastro-intestinal disturbance, fits, or defective vision in the past history.

P. C. (1st admission). Poor physique, thin, pale, rather sallow complexion, with slight puffiness under the eyes, particularly in the early morning. No sign of syphilis, blood W. R. negative. Marked cardiac hypertrophy; pulse small and wiry, no appreciable thickening of the radial artery. B. P., systolic 190 mm. Hg, diastolic 150 mm. Hg. Optic disks normal. Urine pale with slight flocculent deposit and slightly turbid, sp. g. 1018-1015, acid. Albumin 0.05-0.2 per cent. (Aufrecht). Centrifugalized deposit contained many hyaline casts, few granular and epithelial casts and W. B. C., no R. B. C. Average output 35 oz. MacLean's urea concentration test in first hour 1.85 per cent. urea, in the succeeding hours 1.3 per cent. Diastase (Dr. Mackenzie Wallis) 10 units. During the month he was in hospital his condition seemed to improve; he had no headache or vomiting, no nocturnal enuresis. His temperature was normal throughout; pulse-rate, 100 on admission, dropped to 70 with rest, and rose later to 90 when he got up. He kept well for six months and then began to suffer from headaches. Four days after their onset he began to vomit, and on the following day he had a fit, became unconscious, and was admitted to hospital (2nd admission). With treatment by lumbar puncture, venesection, and alkalinization the boy recovered from this attack of uraemia; the condition gradually recurred and he died six weeks after admission of uraemia. During this period of treatment the following observations were made: B. P. 215/160. C. S. F. urea 60 mg. per cent. (Dr. Canti). Urine pale, turbid, sp. g. 1005. Trace of

albumin. Centrifugalized deposit contained a few hyaline casts and occasional W. B. C. Later albumin 0.15 per cent. (Aufrecht), sp. g. 1012-1010. Many subsequent specimens of urine were examined without finding any casts or W. B. C. Optic disks showed patches of exudate in both retinae. Diastase in urine 5 units. Urine culture and blood culture negative. Blood count: R. B. C. 2,960,000. Hb. 48 per cent. C. I. 0.8. W. B. C. 6,400.

Post-mortem, 20.10.20. Uraemia. Chronic nephritis. Pale, wasted, under-sized body showing petechial haemorrhages in the skin of the trunk and limbs, particularly grouped about the umbilicus. Examination of the head and neck not allowed.

Heart. $7\frac{1}{2}$ oz. Muscle pale and firm, hypertrophy of left ventricle, endocardium and pericardium normal. *Vessels* very free from disease. The aorta was almost free from any arterio-sclerotic change. It showed medial hypertrophy, as did the other arteries. In the left coronary artery there was a single plaque of sclerosis. The renal arteries were normal in structure, but the left was double and the right bifurcated at a distance from the kidney.

Kidneys. Each weighed $2\frac{1}{4}$ oz. They were not adherent to the perirenal tissues and the capsule was little thickened; it stripped readily, leaving a shiny granular surface brownish red in colour. The organ was unduly resistant on section; the pelvis somewhat increased in size, not inflamed. Cortex diminished in thickness, lack of distinction in colour between cortex and medulla, the cortex had a confused appearance with loss of distinction in the normal details of structure; cut surface mottled brownish colour with paler areas, and showing minute points of fatty or fibrous tissue. Cut vessels not unduly prominent; the *ureters* were hypertrophied. No hypertrophy of the bladder; a few petechial haemorrhages under its mucous membrane. Marked *suprarenal* hypertrophy with adenomatous overgrowth of the cortex and increase in the medulla.

Histology. Characteristic changes of chronic nephritis of an advanced type. Parenchymatous and interstitial changes were equally prominent. There was uniform affection of the glomeruli of varying degree; the characteristic change was a proliferation of the epithelial layer of Bowman's capsule with heaping up of the cells and adhesion of the parietal and visceral layers; hyaline swelling of some of the capillary loops of the tuft, with fatty degeneration of some. A few had gone on to more complete hyaline degeneration and fibrosis. The majority showed some degree of hyperplasia; there was little pericapsular fibrosis. Tubule changes were marked. The ordinary degenerative changes were present, with atrophy and dilatation of the convoluted tubules, fatty degeneration of the secreting cells in some areas; tubule regeneration was very considerable. The interstitial tissue was increased, there was a patchy small-cell infiltration, and the vascular changes were marked (diffuse hyperplastic sclerosis). No amyloid changes were present. *Vide Plate 3.*

Case IV. Female, aged 14, admitted to hospital under the care of Mr. Foster Moore on account of difficulty of vision increasing during the last month.

H. P. C. Scarlet fever ten months previously. Seemed to have made a good recovery from this; on close questioning there was evidence of loss of health since three to four months previously, in particular loss of energy and unusual fatigue. Since that date had complained at times of headache, cramps in the abdomen, and pains in the arms; during the last week severe headaches and occasional vomiting. No history of oedema, haematuria, dyspnoea, or fits.

P. C. Well developed, rather wasted, pale, dry skin and general diffuse pigmentation; uraemic odour in breath. Cardiac hypertrophy, present but not pronounced; clinical evidence of slight aortic regurgitation and possibly mitral regurgitation. Radial artery not thickened. B. P. 165/123. Optic disks: Marked retinitis and some haemorrhages in left eye; two small patches of degeneration in right. Both disks swollen; haemorrhages in right disk and one

or two small haemorrhages peripherally; exudate along vessels, and star figure at left macula. Urine pale, smoky, sp. g. 1008. Albumin plus. Centrifugalized deposit contained R. B. C. and R. B. C. casts. Blood urea 400 mgm. per cent. Blood culture negative. Blood count: R. B. C. 2,350,000. Hb. 40 per cent. C. I. 0.9. W. B. C. 3,800.

Ulcerative stomatitis developed rapidly; vomiting increased; petechial haemorrhages appeared in the skin and there was bleeding from the uterus. Pericarditis developed a few days before death. The patient died of uraemia.

Post-mortem. Height of child, 4 ft. 2 in. Well-developed body, no skeletal deformity; thin. No axillary or pubic hair.

Heart $8\frac{3}{4}$ oz. Recent general pericarditis with serous effusion. Some hypertrophy of left ventricle, thickening of aortic cusps, and slight thickening of mitral cusps. No recent endocarditis. *Vessels* practically free from arterio-sclerosis, in particular the arteries at the base of the brain, middle, anterior and posterior cerebral arteries, carotids, iliacs, coeliac axis, splenic and superior mesenteric arteries normal. Aorta throughout normal except for a few fatty streaks in the ascending aorta. *Kidneys*: extreme degree of chronic nephritis. Right $\frac{3}{4}$ oz., greatly shrunken. Left $2\frac{1}{2}$ oz. Both adherent to perirenal tissues. Capsule stripped easily, leaving a smooth coarsely granular surface, knobbly and irregular, with bossing and in general a somewhat globular form. Colour pale, the depressions between the granules darker in colour. Cut with resistance; cut surface all trace of normal structure gone. Pelvis much increased, and in some parts extended nearly to the surface. Cortex existed as a whitish streak between atrophied pyramids, and contained retention cysts the size of a small pea filled with a yellow gelatinous fluid. Thickening of renal arteries, but no pouting of vessels on cut surface of kidney. *Suprarenals* hypertrophied.

Histology. An active state of chronic nephritis. The microscopical appearances need not be given in detail as they closely resembled those seen in Case III, except that they were more active. The active proliferation of the epithelial cells of Bowman's capsule was pronounced, tubular hypertrophy was less prominent, and the degenerative changes in the tubules more marked. There was an increase in the interstitial tissue and intense small-cell infiltration. The active state of these and the renal lesion was probably associated with the presence of a terminal secondary infection. The picture was entirely comparable to that seen in adult cases dying of chronic nephritis. The vascular lesion was well marked, and was that of diffuse hyperplastic sclerosis. See Plate 5.

The presence or absence of a lesion of the intimate vasculature of the organs examined microscopically is given in the following table:

Organ.	Case I.	Case II.	Case III.	Case IV.
Kidney	Marked	Present	Marked	Marked
Spleen	Marked	Not examined	Marked	Marked
Suprarenal	Present	Present	Present	Present
Pancreas	Present	Not examined	Present	Present
Small intestine	Present	Present	Not examined	Absent
Large intestine	Present	Present	Not examined	Absent
Stomach	Slight	Present	Not examined	Absent
Liver	Slight	Not examined	Slight	Absent
Lungs	Absent	Not examined	Slight	Absent
Thyroid	Absent	Absent	Not examined	Not examined
Brain	Slight, atypical	Absent	Not examined	Not examined
Heart	Slight, atypical	Absent	Absent	Absent

The radial artery was examined in Case I, and apart from medial hypertrophy was found to be normal.

*Identity of the Vascular Lesion found in these Children with
Diffuse Hyperplastic Sclerosis in Adults.*

In the first place the actual lesion as it affects the terminal arterioles and their parent vessels (best seen in the kidneys) is the same as diffuse hyperplastic sclerosis in adults (10). There is swelling and fatty degeneration of the intima of the arterioles, leading to a greater or less degree of obliteration of the arteriole lumen; frequently the lumen appears to be completely obliterated. At the same time there is proliferation of the intima without fatty degeneration in the parent vessels of the arterioles. Secondly, the vascular lesion affects the intimate vasculature of the organs rather than the larger arteries. This distribution of the lesion within the vascular tree is well illustrated by the present four cases, in three of which the larger arteries are inappreciably diseased, while in the fourth (Case I) it is only the aorta and vessels at the base of the brain that showed much sclerosis. Thirdly, the incidence of the lesion in the various organs follows that found in adults in its main features; that is to say, the kidney and spleen are most affected, the pancreas and suprarenals are next in order, the affection of the intimate vasculature of the liver is slight and the heart escapes. It is noted that the vessels in the brain were not affected in these cases, whereas those in the stomach and intestines were. In these two respects the incidence of the lesion is different to that in adults. The finding of the lesion in the stomach and intestines is interesting because in my experience the lesion is infrequent in this situation in adults; its absence in the brain is only referred to for the sake of fairness, since in only two of the four cases was the brain examined, and in one of these the material was poor. Fourthly, and lastly, the vascular lesion was associated with left ventricular hypertrophy and a raised blood-pressure. *These several points establish the identity of diffuse hyperplastic sclerosis in children and adults.*

Part played by the Endothelium in Intimal Proliferation.

In material taken from adults I have not been able to demonstrate *active* endothelial proliferation in diffuse hyperplastic sclerosis. In some specimens the shadows of endothelial cells that had undergone fatty degeneration were visible (12). In these children, however, examples have been found of the earlier active phase of this lesion (*vide* Plate 3). These specimens, therefore, supply further histological evidence that diffuse hyperplastic sclerosis is an active inflammatory lesion, and complete the link between arterio-sclerosis and such obvious endarteritis as is seen in tuberculosis and syphilis.

Whereas in adults the arterioles seemed to undergo a swelling of their intima with subsequent fatty degeneration leading to obliteration of the lumen, while the parent vessels showed active proliferation of the intima without fatty degeneration, these specimens taken from children seem to show that an earlier

phase of the arteriole lesion has escaped observation in adults; that, in fact, the arteriole lesion is primarily one of active cellular proliferation similar to that which occurs in the parent vessels, and that the cells which proliferate are the endothelial cells.

The Bearing of these Observations on the Aetiology of Arterio-sclerosis.

The conclusion arrived at from the study of these cases, that arterio-sclerosis in children and adults is identical, is not in itself an original observation. In his article on arterio-sclerosis in the *Text-book of Diseases of Children* (Garrod, Batten, and Thursfield) Dr. Poynton makes the same statement. The histological observations made in these cases, however, not only confirm the previous work of others, but go a step farther in that they demonstrate the identity of a particular type of arterial lesion, diffuse hyperplastic sclerosis, in children and adults. This identity is confirmed in detail in the nature of the lesion of the arterial wall, its distribution in the vascular tree and its incidence in the several organs, and its association with a raised blood-pressure and left ventricle hypertrophy. Arterio-sclerosis in general terms is not an uncommon lesion in children; it is known to result from acute infections and from syphilis, and to occur in association with kidney disease. By defining the particular type of arterial lesion present in a case the problem of its causation is in a degree simplified, and it is for future observation to determine whether this particular type of arterio-sclerosis occurs in syphilitic children apart from kidney disease, whether it can be caused by acute infections apart from kidney disease, whether in fact it ever occurs in children without simultaneous disease of the kidneys.

It is possible that by the definition of diffuse hyperplastic sclerosis in children this problem of the association of arterio-sclerosis with chronic nephritis may be simplified in another direction. Hitherto it has been difficult to account for the presence in some cases and the absence in others of a raised blood-pressure and cardiac hypertrophy. Thus Miller and Parsons (4) in describing the cases of their first group with renal disease write: 'Cases in this group have many similarities and only two points of difference; these latter consist of the presence or absence of cardio-vascular changes, and the age at which the symptoms were first noticed. These clinical differences are of considerable interest, which is enhanced by the fact that *they do not appear to correspond to any pathological differences.*' (Italics mine.) This may be true so long as microscopical study of these cases is limited to the kidneys, but if the pathology of the disease in children follows the line that it appears to in adults, it may be found that in those patients without cardiac hypertrophy and raised blood-pressure the vascular lesion (in so far as it affects the intimate vasculature of organs) is practically limited to the kidneys, whereas in those cases with a raised blood-pressure and cardiac hypertrophy the vascular lesion is widely distributed, as it was found to be in the present series.

It cannot be said that the present observations throw any new light on the nature of the association of chronic nephritis and arterio-sclerosis. The endothelial proliferation seen in arteriole walls, of which these are believed to be the first examples seen in diffuse hyperplastic sclerosis, is further histological evidence of the active inflammatory nature of this vascular lesion. Further, the active inflammatory change observed in the kidneys of all four cases, particularly the proliferation of the epithelial cells of Bowman's capsule, is evidence of a primary affection of the renal parenchyma, and it is suggested that proliferation of such specialized cells would not result from the starvation of a glomerulus of its blood supply; it indicates, in fact, that the renal lesion is primary and not the secondary result of vascular disease. It is equally difficult to interpret the vascular lesion as a direct result of renal disease in this limited sense that the vascular lesion is one of arterial involution. For in the first place, as previously shown (11), fatty degeneration is not a part of the histological picture of involution; and in the second place such a point of view will not explain the wide distribution of the vascular lesion in these four cases. At present, the simplest conception is to regard the vascular and renal lesions as simultaneous results of the action of a single pathogenic agent.

There remains, however, another interpretation, namely, the possibility that renal disease indirectly causes arterial disease, perhaps through the toxæmia that inefficient renal function produces. Such an interpretation is suggested by the unique case reported by Hale-White (13), in which, in a boy aged 6 months, the most extensive and unusual type of arterio-sclerosis was associated with bilateral hydronephrosis and extreme cirrhosis of the kidneys due to phimosis. The author was of the opinion that syphilis was the main aetiological factor in this case, and that the kidney disease was a contributory cause.

As regards these two aetiological factors in the present cases it is unlikely that syphilis played a part. Except in Case II, whose birth was preceded by four miscarriages, there was nothing in the past or family history of the patients to suggest syphilis; there was no clinical sign of syphilis and the blood Wassermann reaction, which was done in Cases I, II, and III, was negative. It is generally agreed that cases of chronic nephritis in children of the particular type to which the present series belong are not syphilitic. The congenital defect of the right kidney in Case II is, on the other hand, some indication of a primary renal affection. It is a commonplace in pathology that congenitally deformed organs are particularly prone to disease, and Dr. Spilsbury, whose help in disentangling the histology of these specimens I gratefully acknowledge, has told me that in his opinion this general statement seems to be especially true of the kidneys. It is possible that congenital polycystic kidneys, which are so often associated with arterial disease, are an example of a primary and congenital renal affection that is responsible for arterial disease. In Case III there was a congenital abnormality of both renal arteries, a fact which may have a similar significance. While these two cases provide anatomical evidence of a congenital defect the clinical history of Case I indicates a very early onset

of the affection; the onset of the complaint, if not congenital, must have been acquired *in utero* or in early infancy.

Scarlet fever remains for consideration as a possible aetiological factor. Case I suffered from scarlet fever, but only after the disease of the kidneys was fully developed, and it did not influence its course. It is possible that scarlet fever initiated the morbid series in Case III; the patient's mother was not a good witness. In Case IV, which differed from the others in its later age of onset and in its more rapid course, it was reasonable to assume that scarlet fever was the responsible cause.

Conclusions.

1. Diffuse hyperplastic sclerosis is identical in children and adults.
2. Its association with chronic nephritis in children is more significant than in adults, because many of the causes of arterio-sclerosis are excluded in children by reason of their age.

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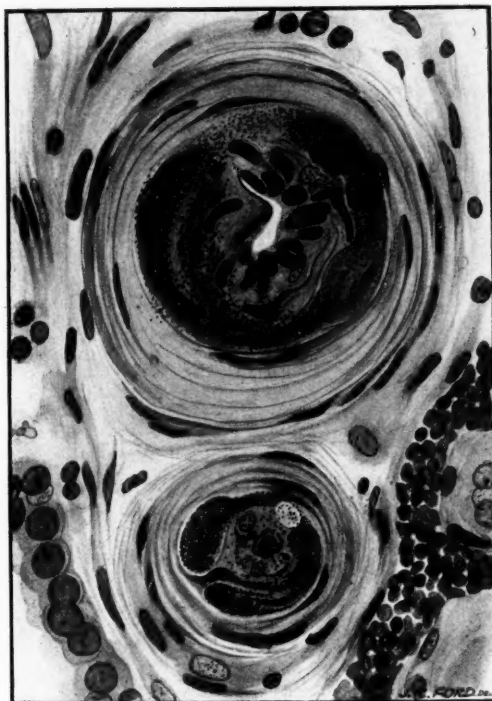
DESCRIPTION OF PLATES.

PLATE 3. Case II. Magnification $\times 480$. The two arterioles shown in cross-section were found in the kidney of Case II. The lumen of the lower arteriole appears to be completely occluded; this is the common appearance in adult diffuse hyperplastic sclerosis. The upper arteriole shows an earlier stage of the same process; multiplication of the endothelial cells has occurred; those situated peripherally are much swollen and have undergone fatty degeneration, while those bordering the lumen have large clearly staining nuclei and seem to be actively proliferating. There is no change in the media, except perhaps some hypertrophy. The section is stained with haemalum and Sudan 3. The fat-staining of those cells which appear filled with fine black dots in this reproduction was intense; the fat-staining was limited to these cells.

Case III. Magnification $\times 480$. An arteriole showing endothelial proliferation in a stage intermediate to that seen in the two arterioles in Case II.

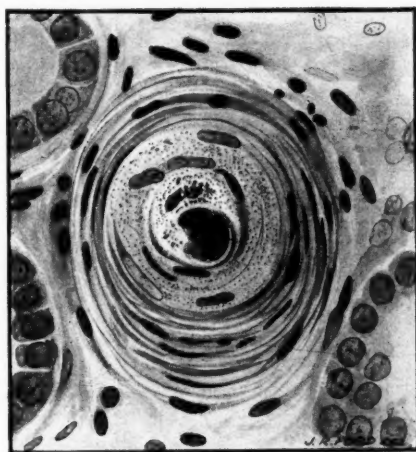
PLATE 4. Case III. Magnification $\times 175$. Section of kidney from Case III showing the changes characteristic of chronic nephritis, except that this particular field does not happen to show any small-cell infiltration. In the left top corner is a glomerulus in which there is confusion of normal structure and decrease in the number of nuclei present due to hyaline degeneration of the capillaries of the tuft; there is heaping up of proliferated epithelial cells of Bowman's capsule into crescent-shaped masses. On the right is a distended empty venule, and adjoining it a degenerated glomerulus sliced across the top. Next to this is one of the vasa recta showing intimal proliferation, below which is an arteriole (vas afferens) with hypertrophied media. The larger artery to the right, cut rather obliquely, shows marked intimal proliferation without fatty degeneration, and in the top right-hand corner is an arteriole characteristic of diffuse hyperplastic sclerosis, its lumen being blocked with a swollen (once proliferated) intima which has undergone fatty degeneration. Half-way down on the left is a patch of oedematous fibrous connective tissue which fills a space left by the atrophy of tubules or glomeruli; next to this are numerous dilated tubules, whose lumen is filled with desquamated cells, hyaline, and granular debris which occasionally takes up a little Sudan 3 stain. The large tubules are examples of tubule hyperplasia; finally, a single partly hyaline and partly fibrotic glomerulus is seen to the right of the centre.

PLATE 5. Case IV. Magnification $\times 275$. These figures show three characteristic forms of glomerular lesion. In this case the interstitial reaction was very marked, and there was a great deal of small-cell infiltration. The glomerulus on the left above shows the endo-glomerulitis characteristic of chronic nephritis; there is hyaline degeneration of the tuft with early fatty degeneration (seen as fine black spots) and proliferation of the epithelial cells of Bowman's capsule. In addition, both in this glomerulus and that to the right, there is pericapsular fibrosis. Hyaline degeneration of the tuft has reached an advanced stage in the second glomerulus. In the third glomerulus the tuft is somewhat shrunken, but the main pathological change is a pericapsular fibrosis.



Case II

x 480



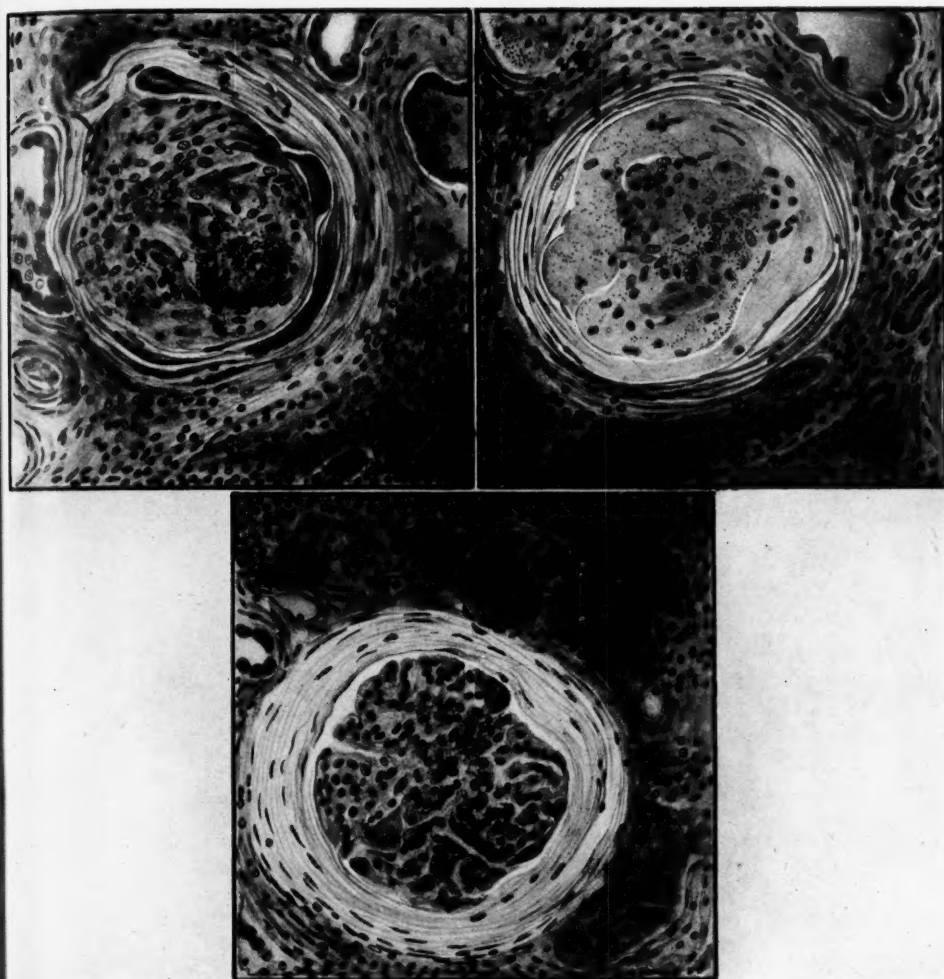
Case III

x 480



Case III

× 175



Case IV

× 275

STUDIES ON CALCIUM AND PHOSPHORUS METABOLISM

PART I. THE EXCRETION OF CALCIUM AND PHOSPHORUS

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IN contrast to the large amount of biochemical work which has been undertaken on general problems affecting nutrition, the process of ossification, which is certainly one of the most important of these, has received but little attention. Most researches on this subject have been concerned with the growth and development of bone on histological lines. Investigations into the nature of the biochemical conditions which govern normal ossification have been few. The earlier observers confined themselves chiefly to studies in the composition of bone, largely restricting their field of inquiry to the distribution of the salts of the bone ash. While much of this work is of fundamental importance, our knowledge of the metabolic changes which finally lead to the deposition of the various salts constituting the mineral matter of formed bone has remained fragmentary.

A study of the process of ossification must necessarily involve consideration of the metabolism of calcium and phosphorus, since these constitute the chief elements of the bone-salts. Recently, attention has been directed to their importance in various pathological processes apart from those involving the skeleton. Bosworth, Bowditch, and Giblin (1), Holt, Courtney, and Fales (2), and others in America have demonstrated the necessity for special consideration of calcium in intestinal disorders in infants.

In spite of the increased stimulus given to studies of the metabolism of calcium and phosphorus by the recognition of their importance in many pathological processes, our knowledge concerning the absorption, transport, utilization, and excretion of these elements in the human subject has advanced somewhat slowly, and much of it is based on data derived from experiments on animals.

The present contribution contains the results of observations on the metabolism of calcium and phosphorus in infants fed on cow's milk. It is presented in two parts: (1) The excretion of calcium and phosphorus is first discussed. For the sake of clearness, the experiments are described in sections as follows: (a) The influence of diet on the amount of faeces excreted. (b) The effects of variation in the intake of calcium and phosphorus on their elimination. (c) The distribution of fatty derivatives in the faeces. (d) The relation of

phosphorus to fat excretion. (2) The relative retentions of calcium and phosphorus in normal and rachitic infants.

(a) *The relation of faecal solids to diet.* In normal infants on a diet of cow's milk, the mineral matter and fatty derivatives constitute together about one-half of the dried faeces, the composition of which is illustrated by the following analyses:

Analyses of Normal Dried Faeces in Infants (per cent.).

	Diet: Cow's milk.				
	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.
CaO	10.9	10.0	10.1	7.8	8.05
P ₂ O ₅	7.7	8.6	7.7	5.75	5.82
Neutral fat	1.07	1.81	1.62	3.5	3.34
Free fatty acids (as oleic acid)	11.13	10.99	10.43	15.2	16.21
Combined fatty acids	19.15	16.35	17.90	17.1	14.2
Total fat	31.35	29.15	29.95	35.8	33.75
CaO as phosphate	8.94	8.34	8.28	6.06	6.61
CaO as soaps	1.96	1.66	1.82	1.74	1.44

Calcium is eliminated almost entirely by the faeces in combination with phosphorus and as soaps, and one of the first considerations to arise in the study of excretion of the two elements is the relation of ingested mineral matter and fats to the faecal solids. According to Lusk (3), 'common observations would seem to justify the popular supposition that normal faeces are made up of the undigested residues of the food-stuffs. In truth, however, this is very far from the fact. The faeces are chiefly the unabsorbed residues of intestinal secretions.' The evidence upon which this conclusion was based was derived from the experimental studies of Voit and others on animals, and from observations during starving experiments on men.

The following experiments were conducted to test the accuracy of this generalization in the particular case of infants fed on cow's milk, by determining to what extent excretion by the bowel was dependent on the amount of milk solids ingested.

Methods: Each subject was placed on a 'metabolism' bed (4) and the urine and faeces collected separately every twenty-four hours, during periods of several days. The faeces were dried on a steam bath, then weighed, finely ground, and preserved for subsequent examination in air-tight stoppered bottles. The data derived from the analyses of these specimens of urine and faeces are discussed in the following sections.

In the initial period the intake consisted of fresh undiluted cow's milk. During the second period one-half of this measured quantity of milk was given, the bulk being kept constant by dilution with water, and the calorific value by addition of cane sugar. Observations over a third period in which the diet consisted of diluted whey (prepared by rennet coagulation) were also made. The reduction of the milk solids in the diet to such a small concentration (fat, 0.8 per cent.: CaO, 0.04 per cent.: P₂O₅, 0.05 per cent.) generally resulted in the

onset of diarrhoea, and consequently abnormal stools. In these cases, the average daily faecal weight was of little importance for comparative purposes and is not recorded in the tables.

TABLE I
Relation of Faecal Weight to Diet.

Case 1. O. M., aged $1\frac{3}{12}$ years. 8.3 kilos.

Period I. Diet: 1,000 c.c. cow's milk daily.

Day	1	2	3	4	5	6	7	8
Weight of dry faeces	21.1	6.9	20.1	18.9	4.7	18.7	7.3	13.6

Average daily weight = 13.9 gm.

Period II. Diet: 500 c.c. cow's milk and 500 c.c. water.

Day	1	2	3	4
Weight of dry faeces	8.9	6.4	2.4	6.8

Average daily weight = 6.1 gm.

Case 2. A. Q., aged $\frac{2}{12}$ year. 6.5 kilos.

Period I. Diet: 1,000 c.c. cow's milk daily.

Day	1	2	3	4
Weight of dry faeces	11.2	16.6	9.2	16.2

Average daily weight = 13.3 gm.

Period II. Diet: 500 c.c. cow's milk and 500 c.c. water.

Day	1	2	3	4
Weight of dry faeces	8.2	6.5	9.1	10.0

Average daily weight = 8.4 gm.

Case 3. R. A., aged $\frac{2}{12}$ year. 9.4 kilos.

Period I. Diet: 1,000 c.c. cow's milk daily.

Day	1	2	3	4
Weight of dry faeces	15.6	18.2	19.6	23.3

Average daily weight = 19.1 gm.

Period II. Diet: 500 c.c. cow's milk and 500 c.c. water.

Day	1	2	3	4
Weight of dry faeces	8.0	10.6	9.8	8.2

Average daily weight = 9.1 gm.

Case 4. A. G., aged $\frac{6}{12}$ year. 6.45 kilos.

Period I. Diet: 1,000 c.c. cow's milk daily.

Day	1	2	3	4	5	6	7
Weight of dry faeces	7.8	4.5	14.5	nil	13.2	21.8	9.5

Average daily weight = 10.19 gm.

Period II. Diet: 500 c.c. cow's milk and 500 c.c. water.

Day	1	2	3
Weight of dry faeces	6.0	3.8	3.6

Average daily weight = 6.1 gm.

Period III. Diet: 500 c.c. whey and 500 c.c. water.

Day	1	2	3	4
Weight of dry faeces	Nil	Nil	2.1	5.8 (enema)

Average daily weight = 1.9 gm.

TABLE I (continued).

Case 5. G. K., aged $\frac{1}{2}$ year. 5.2 kilos.

Period I. Diet: 1,000 c.c. cow's milk daily.

Day	1	2	3
Weight of dry faeces	17.2	19.8	18.6

Average daily weight = 18.5 gm.

Period II. Diet: 1,000 c.c. whey daily.

Day	1	2	3
Weight of dry faeces	3.5	2.3	5.3

Average daily weight = 3.7 gm.

Case 6. J. C., aged $\frac{1}{2}$ year. 5.6 kilos.

Period I. Diet: 780 c.c. cow's milk daily.

Day	1	2	3	4	5	6
Weight of dry faeces	10.8	11.0	11.8	14.1	14.0	20.9

Average daily weight = 13.7 gm.

Period II. Diet: 780 c.c. cow's milk daily and 1.0 gm. CaO as calcium lactate.

Day	1	2	3	4
Weight of dry faeces	18.3	26.0	29.0	12.7

Average daily weight = 21.5 gm.

Results: It will be seen that the daily average weight of dried faeces shows a definite decrease with the diminished intake of milk solids. When the solids of the milk in the diet were halved, the faecal weight as shown in the second period was found to be correspondingly reduced. The effect of reducing the milk solids in the intake by using diluted whey is strikingly shown in Case 4, in which no diarrhoea resulted. On the last day of this period the contents of the large intestine were washed out by means of a plain water enema. The substitution of whey for the diet of unmodified cow's milk in Case 5 resulted also in an extreme reduction of the weight of faeces.

Bischoff and Voit (quoted by Lusk, *loc. cit.*) found that the production of faeces in dogs was not proportional to the amount of meat ingested. The faeces of herbivora, however, consist largely of undigested residues of the food, and consequently the weight of dry faeces depends on the intake of solids.

The conclusion to be drawn from the results recorded is, that in infants on a diet of cow's milk the production of faeces also depends on the amount of milk solids of the diet. In each case non-nitrogenous matter in the form of calcium phosphate, calcium soaps, and fatty derivatives formed about one-half of the faecal solids, and, consequently, the reduction of the average daily faecal weight observed must have been largely due to a correspondingly reduced evacuation of these from the bowel.

It was therefore of importance to ascertain how much of the non-nitrogenous matter of the faeces was derived directly from the elements of the milk solids. Further observations were accordingly made on the elimination of calcium,

phosphorus, and fats in relation to the amounts of these ingested, with the object of studying the conditions which govern their excretion. The large proportion of calcium salts in the non-nitrogenous matter of the faecal solids suggested that the amount of this element in the diet was one of the chief factors in influencing the faecal weight, e.g. the effect of adding 1 grm. of CaO daily (as calcium lactate) to the intake in Case 6 was a pronounced increase in the average weight of dried faeces excreted per day.

(b) *The effects of variation in the intakes of calcium and phosphorus on their elimination.* In the preceding series of experiments the mineral content of the diet during the first period (unmodified cow's milk) was double that of the second period (diluted milk) and approximately five times that of the third (diluted whey). Considerable variations were therefore made in the amounts of CaO and P_2O_5 ingested during these periods. The effects of variations in the intake thus made on the excretion of calcium and phosphorus, and on faecal weight, were also studied in two additional experiments. In one of these calcium was omitted almost entirely from the intake; in the other an attempt was made to ascertain the influence of fat and soluble phosphate on faeces formation, by their addition separately to a diet deficient in both.

Method: Faeces and urine were collected as already described. The total CaO and P_2O_5 in the diet and the excreta corresponding to each period were determined, the estimations being made by the usual gravimetric methods. The following results were obtained:

TABLE II.

Relation between the Amounts of Calcium and Phosphorus ingested and excreted (per Day).

Case.	Period.	Intake.		Weight of Dried Faeces.	Urine.		Excretion.			
		CaO grm.	P_2O_5 grm.		CaO grm.	P_2O_5 grm.	CaO grm.	Faeces.		
								%	P_2O_5 grm.	%
I										
1. O. M. $1\frac{3}{4}$ years	8 days cow's milk	1.65	2.2	13.9	—	1.17	1.6	11.5	1.05	7.35
II										
	4 days diluted milk	0.82	1.1	6.1	—	0.93	0.67	11.1	0.33	5.43
I										
2. A. Q. $1\frac{1}{2}$ year	4 days cow's milk	1.65	2.2	13.3	0.003	0.93	1.22	9.2	0.94	7.06
II										
	4 days diluted milk	0.82	1.1	8.45	0.002	0.59	0.68	8.05	0.49	5.82
III										
	4 days whey	0.50	0.55	dia- rrhoea	0.002	0.43	0.16	1.61	0.04	0.43

[Q. J. M., Oct., 1922.]

F

TABLE II (continued)

Case.	Period.	Intake.		Weight of Dried Faeces.	Urine.		Excretion.			
		CaO gram.	P ₂ O ₅ gram.		CaO gram.	P ₂ O ₅ gram.	CaO gram.	%	P ₂ O ₅ gram.	%
3. R. A. 1½ year	I 4 days cow's milk	1.6	2.0	19.1	—	0.92	1.36	7.1	0.74	3.9
	II 4 days diluted milk	0.80	1.0	9.1	—	0.56	0.56	6.2	0.24	2.68
	III 4 days diluted whey	0.3	0.4	diarrhoea	—	0.25	0.23	1.9	0.11	0.9
	IV 3 days sugar and butter fat	0.02	0.02	diarrhoea	—	0.2	0.04	0.54	0.03	0.47
	V 3 days sugar and butter fat + 0.1 gram. CaO as calc. lactate	0.13	0.02	stools solid	—	0.05	0.14	0.69	0.06	0.30
	VI 3 days sugar and butter fat + 0.2 gram. CaO as calc. lactate	0.29	0.02	stools solid	—	Nil	0.29	1.9	0.05	0.35
4. A. G. 1½ year	I 7 days cow's milk	1.62	2.05	10.19	0.027	0.78	1.52	14.27	1.11	10.93
	II 3 days diluted milk	0.81	1.02	6.1	0.016	0.60	1.0	16.5	0.67	11.09
	III 3 days diluted whey	0.3	0.44	1.9	0.006	0.40	0.28	14.5	0.21	10.8
5. G. K. 1½ year	I 3 days cow's milk	1.66	2.22	18.5	0.024	0.40	1.48	8.05	1.45	7.89
	II 3 days diluted whey	0.21	0.43	3.7	0.02	0.25	0.18	5.5	0.24	6.55
	III Diluted whey + 1.8 gram. CaO as calc. lactate	2.01	0.43	4.9	0.032	0.10	1.03	20.9	0.27	5.88
	IV Diluted whey butter fat + 1.8 gram. CaO as calc. lactate	2.01	0.43	10.0	0.034	0.08	1.88	15.5	0.37	3.77
	V Diluted whey butter fat + 1.8 gram. CaO as calc. lactate + 1.25 gram. P ₂ O ₅ as NaH ₂ PO ₄	2.01	1.68	10.2	0.16	0.22	1.42	13.45	0.89	8.44
6. J. C. 1½ year	I Cow's milk 3 days	1.28	1.71	13.7	0.008	0.61	1.24	11.15	0.85	8.05
	II Cow's milk + 1.0 gram. CaO as calc. lactate	2.28	1.71	21.5	0.12	0.39	1.72	8.05	0.92	4.32

In each period the amounts of CaO and P_2O_5 ingested daily are compared with those found in the excreta, and with the corresponding average daily weight of dried faeces. It is hardly necessary to state that values for the retentions of the two elements cannot be derived from the data presented, since these are not balance experiments in a quantitative sense (see Part II, p. 65).

An examination of Table II shows that in all the periods, the elimination of CaO and P_2O_5 was simply dependent on the amounts of these in the diet, and further that with diminished intake there was a corresponding diminution of calcium and phosphorus in both urine and faeces. The variation in the average daily weight of dried faeces with the calcium content of the diet is also noteworthy. During the periods when the amount of calcium ingested was small, diarrhoea often ensued. The stools in these cases were abnormal owing to the escape of an excess of fatty derivatives, and the weight of faeces was not recorded.

Case 1. The percentage CaO of the dried faeces is almost the same in both periods, while the reduction in faecal weight during the second period is nearly proportional to the diminution in the amount of CaO ingested.

Case 2. The percentage of CaO during the second period is slightly less than that of the first. The difference is not proportional to the variation in the intake, however. The reduction in faecal weight again approximately corresponds to the diminution of CaO ingested. In Period III there was diarrhoea. The low values for the percentages of CaO and P_2O_5 in the faeces recorded are here, as in the other experiments, due to an excess of fatty derivatives in the faeces.

Case 3. The first three periods present the same features as in Case 2. In Period IV the diet was practically free from calcium and phosphorus. The stools were fluid. The extreme reduction of the two elements in the faeces is correlated with the low intake, the excretion of calcium especially being almost negligible over a period of three days. The ash of the dried faeces during this period was easily fusible and appeared to consist chiefly of alkaline salts. This result shows that there was practically no calcium excreted from endogenous sources, and extremely little phosphorus, if any.

The addition of a comparatively small quantity of calcium (0.1 gm. CaO) daily to the diet in Period V immediately resulted in the faeces becoming white and semi-solid. In this and the succeeding period (0.2 gm. CaO added) the corresponding increase in the excretion of calcium by the faeces is evident. With the addition of calcium to the diet of Period IV, the urine finally became phosphorus free. It should be noted that although the addition of the small quantities of calcium to the diet during Periods V and VI changed the consistency of the faeces from a fluid to a semi-solid condition, there was still an excessive loss of fat by the bowel. This change in the nature of the faeces is discussed later, when it will be shown to have been due to an increased formation of calcium soaps.

Case 4. No diarrhoea occurred during Period III (diluted whey) in this case, and the effects of reduction in the intake of CaO and P_2O_5 are clearly illustrated. The percentage of CaO and P_2O_5 in the dried faeces remained practically constant throughout the whole experiment, while the average daily weight of dried faeces was reduced in proportion to the amount of CaO ingested. The reduction of the calcium and phosphorus in both urine and faeces with the diminished intake is again to be observed.

Case 5. During the first period, the average weight of dried faeces was very high (18.5 gm.). The mineral matter in the intake and the fat were

excessively reduced in Period II by diluting the whey of the diet to twice its volume with water. The intake of fat was only 3.9 gm. per day. The extreme reduction of the faecal weight (3.7 gm.) will be observed.

The effects of an excess of a soluble calcium salt in a diet deficient in fat and mineral matter were followed by adding 1.8 gm. of CaO as calcium lactate to the diluted whey (Period III). Since the combining weight of fatty acids is approximately ten times that of calcium in the formation of calcium soaps, there was a large excess of CaO in the diet above that required to combine with all the fatty acids and phosphoric acid derivable from the diluted whey. Interest centred therefore in the mode of excretion of calcium during this period, and particularly in the question as to whether an excess of calcium induces a compensatory increased secretion of phosphoric acid into the intestine.

The dried faeces obtained were brick-hard, and effervesced strongly in dilute hydrochloric acid. Subsequent examination showed that about 70 per cent. of the total CaO of the dried faeces existed as carbonate of lime. The large increase of the percentage of CaO in the faeces is also striking. The amount of phosphoric acid excreted by the intestinal route was practically the same as that of the preceding period, though the urinary phosphorus was less. There was a slight increase in the urinary calcium. In spite of the large increase of calcium salt in the diet practically no change in the average daily weight of dried faeces resulted, and in order to ascertain whether this was due to the relative absence of fat or phosphoric acid in the diet, additions of these were made separately over the two subsequent periods.

During Period IV 15 gm. of milk fat were added daily to the diluted whey diet of Period III, the calcium content being unaltered. The average daily weight of dried faeces rose immediately from 4.9 gm. to 10.0 gm. On examination of the distribution of fat in the faeces (see later) it was found that nearly all the calcium of the faeces was in combination with fatty acids. No carbonate of lime was found.

An attempt was again made to increase the average daily weight of dried faeces by the addition of an excess of a soluble phosphate to the diet (Period V). 1.25 gm. of phosphoric acid as NaH_2PO_4 were added daily to the diet of Period IV.

The percentage of P_2O_5 in the faeces was increased though a portion of the added phosphorus had been excreted by the urine. The calcium content of the urine was considerably increased, probably, as Ott has stated, by the elimination of the calcium as CaHPO_4 . The faecal weight remained unaltered.

Case 6. This experiment consisted essentially in following the effects of an excess of calcium added to a diet containing adequate quantities of fat and phosphoric acid. In both periods the same amount of unmodified cow's milk was given, 1 gm. of CaO as calcium lactate being added daily to the intake during the second period. The effects produced by the addition of the calcium salt were the same as those observed in previous experiments. There was a considerable increase of faecal weight. More phosphoric acid was excreted by the faeces, and consequently less by the urine. An increased elimination of calcium by the urine as well as by the faeces occurred. There was a notable fall in the percentages of CaO and P_2O_5 in the dried faeces during the second period. This was subsequently found to be due to the presence of an increased amount of fatty derivatives.

Discussion. From these results there would appear to be little doubt that in infants fed on cow's milk the amount of calcium and phosphorus eliminated depends on the amounts ingested. With a diminution in the intake there was a corresponding fall in the amounts excreted, and when calcium and phosphorus

in the diet were reduced to minute quantities, the amounts of the two elements found in the excreta were correspondingly small.

When an excess of calcium salt was present in the diet there was an increased excretion of calcium by the faeces and a slight rise in the urinary calcium. The increase of calcium in the urine indicated that increased absorption had occurred. R. Berg (5), who investigated the retention of different calcium salts, found that the excretion of the excess took place almost entirely by the intestinal route.

The effect of an excess of calcium in the diet on the excretion of phosphorus is clearly shown. More phosphoric acid was found in the faeces and less in the urine. The calcium therefore served to restrict the phosphorus to the intestinal contents.

These conclusions confirm the work of previous observers on the elimination of calcium and phosphorus. An exhaustive review of the literature on the subject has been made by Forbes and Keith (6), from which the following references are taken. The decrease by one-half in urinary phosphorus, following the ingestion of 10 grm. of carbonate of lime per day, was found by Riesell, who experimented on himself. Similar observations were made by Lehmann, Strauss, and Herxheimer. Rüdell showed that the administration of calcium carbonate to children caused an increase in the urinary calcium, but not in proportion to the intake. Kochmann and Petsch working on dogs found that an increase of lime in the diet was followed by an increase of faeces phosphorus and a diminution of urinary phosphorus. Similar results were obtained by Bertram and Renvall. In an experimental study of calcification in dogs, with D. Noel Paton, the writer found that 88 per cent. of the phosphorus ingested was excreted by the urine. On the same diet, with the addition of a large excess of calcium lactate, only 15 per cent. of the ingested phosphorus appeared in the urine, a greatly increased amount being eliminated by the faeces.

By the addition of a large excess of calcium to a diet deficient in fat and phosphorus, the urine could be rendered phosphorus free, most of the ingested phosphorus being restricted to the intestine, and the excess of calcium eliminated by the faeces as carbonate.

Finally, the influence of calcium in the diet in controlling the amount of faecal solids excreted has been shown to be very great. This effect is apparently dependent chiefly on calcium soaps, and therefore on the extent of the combination of the ingested calcium with fatty acids in the intestine. It did not occur in the absence of an adequate amount of fat in the diet, or in the presence of an excess of phosphoric acid.

(c) *The distribution of fatty derivatives in dried faeces, and the relation between calcium soaps and faecal solids.* The distribution of the fatty derivatives is of interest in view of the governing influence which calcium soaps possess on excretion by the bowel. One of the best illustrations of the effects of an excess of calcium soap formation in the intestine is seen in jaundice. In a case of congenital obliteration of the bile ducts (7) studied by the writer, in which

fat-splitting was not appreciably diminished, though there was a persistent excess of free fatty acids in the intestine from non-absorption of digested fat, the average daily weight of dried faeces was consistently more than double that of a normal infant of the same age when the diets of unmodified cow's milk were identical. It was found that about 80 per cent. of the total calcium of the faecal solids was combined with fatty acids in the case of biliary atresia; the normal faeces contained only 20 per cent. of the total calcium in this form.

Examination of the distribution of the fatty derivatives in the dried faeces collected in the preceding experiments were made chiefly with the object of ascertaining the relation between the average daily weight of faecal solids and the amount of calcium soaps these contained.

Method: The neutral fat and free fatty acids were extracted directly with ether. After drying and weighing, the mixture was dissolved in neutral alcohol and the free acids titrated with $\frac{N}{10}$ NaOH, the latter being calculated to oleic acid. The neutral fat was found (approx.) by difference. The combined fatty acids were obtained from the residue of the first extraction by splitting the insoluble soaps with dilute hydrochloric acid and extracting with ether in a separating funnel. The weight of calcium soaps in the dried faeces was then calculated from the combined fatty acids, the mean molecular weight of these being taken as 274.0.

It has been shown by Holt *et al.* (2), who determined the distribution of fatty derivatives in dried and moist samples of a composite stool, that in the process of drying practically no change in composition occurs in the faeces of infants fed on cow's milk. The following results were obtained:

TABLE III

The Distribution of Fatty Derivatives and the Relation between Calcium Soaps and Faecal Solids.

Case 1. No analysis made of the faecal solids.

Case 2. A. Q.

	Period I.	Period II.	Period III.
	Milk.	Diluted Milk.	Whey.
Neutral fat	6.57	3.34	32.93
Free fatty acids (as oleic acid)	17.58	16.21	30.91
Combined fatty acids	17.10	14.2	3.12
Total fats	41.25	33.75	66.96
Average daily weight of faecal solids	13.3 grm.	8.4 grm.	Diarrhoea
Weight of calcium soaps excreted daily	2.41 grm.	1.26 grm.	—

TABLE III (continued).

Case 3. R. A.

	Period I.	Period II.	Period III.	Period IV.	Period V.
	Milk.	Diluted Milk.	Whey.	Whey + 0.1 gm. CaO as calc. lactate.	Whey + 0.2 gm. CaO as calc. lactate.
Neutral fat	2.13	3.10	14.9	51.63	40.04
Free fatty acids	17.62	12.4	25.9	27.07	22.56
Combined fatty acids	31.2	21.7	5.9	9.4	13.0
Total fats	50.95	37.2	46.7	88.10	75.6
Average daily weight of faecal solids	19.1 gm.	9.1 gm.	Diarrhoea	Semi-solid stools	Semi-solid stools
Weight of calcium soaps excreted daily	6.30 gm.	2.11 gm.	—	—	—

Case 4. A. G.

	Period I.	Period II.	Period III.
	Cow's Milk.	Diluted Milk.	Whey.
Neutral fat	1.9	2.9	3.4
Free fatty acids	3.3	4.2	1.7
Combined fatty acids	31.2	35.2	20.1
Total fats	36.4	42.3	25.2
Average daily weight of faecal solids	10.19 gm.	6.1 gm.	1.9 gm.
Weight of calcium soaps excreted daily	3.26 gm.	2.2 gm.	0.3 gm.

Case 5. G. K.

	Period I.	Period II.	Period III.	Period IV.	Period V.
	Milk.	Whey.	Whey + 1.8 gm. CaO as calc. lactate.	Whey + 1.8 gm. CaO + butter fat.	Whey + 1.8 gm. CaO + butter fat + 1.2 gm. P_2O_5 as NaH_2PO_4 .
Neutral fat	3.0	1.2	0.81	2.0	1.7
Free fatty acids	21.1	5.1	0.49	3.6	7.6
Combined fatty acids	16.1	24.4	9.2	30.1	33.9
Total fats	40.2	30.7	10.5	35.7	43.2
Average daily weight of faecal solids	18.5 gm.	3.7 gm.	4.9 gm.	10.0 gm.	10.2 gm.
Weight of calcium soaps excreted daily	3.15 gm.	0.94 gm.	0.42 gm.	3.15 gm.	3.67 gm.

Case 6. J. C.

	Period I.	Period II.
	(Milk.)	(Milk—1 gm. CaO as calc. lactate.)
Neutral fat	1.7	3.2
Free fatty acids	10.2	15.4
Combined fatty acids	29.6	26.6
Total fats	41.5	45.2
Average daily weight of faecal solids	13.7	21.5
Weight of calcium soaps excreted daily	4.3 gm.	6.1 gm.

Case 1. The distribution of the fatty derivatives was not determined in this case owing to accidental loss of the specimens.

Case 2. The excretion of total fat during the first period was slightly above the normal. The distribution of fatty derivatives during the second period shows that only minor changes in composition resulted when the intake of milk solids was reduced by one-half, the chief one being a reduction of the total fatty derivatives. The fall in faecal weight and diminution of calcium soaps are seen to be roughly proportional to each other. In Period III diarrhoea ensued, and the faecal weight was consequently without quantitative significance. The large excess of neutral fat and free fatty acids found in the faeces is characteristic of diarrhoea and is evident in all the other cases of the series. Correlated with the excessively reduced intake of calcium during this period, the percentage of combined fatty acids and therefore of calcium soaps in the faecal solids is very low.

Case 3. In Period I the percentage of total fat is again abnormally high, and especially the combined fatty acids. The distribution of the fatty derivatives in the second period is, in this case, appreciably different from that of the first, and a strict correspondence between the reduction in faecal weight and calcium soaps was therefore not to be expected. The correlated fall in each of these with the reduced intake is fairly well shown, however. Diarrhoea ensued in the third period, and the distribution of the fatty derivatives presented all the features described in the preceding case. In Period IV the stools were rendered pasty in consistency on the addition of 0.1 gm. CaO as calcium lactate. In this and the succeeding period there was still an escape of a large excess of neutral fat and free fatty acids as in diarrhoeal stools in spite of the changed consistency of the faeces. The increase of combined fatty acids and therefore of calcium soaps in both periods is again correlated with the increasing additions of calcium to the diet. It would seem as if the increased formation of calcium soaps in the two last periods had been responsible for the physical change in the nature of the faeces. In this way the therapeutic effects of calcium salts in diarrhoea may be explained.

Case 4. The effects of the variations made in the intake are well illustrated in this case. The distributions of the fatty derivatives in the faeces of the first two periods show but slight differences; the notable result is the reduction of the faecal weight with the calcium soaps. The diminution in faecal weight and calcium soaps during the third period, following the substitution of whey for diluted milk in the diet, is very pronounced. The fall in percentage of combined fatty acids and total fat in this period is again correlated with the low content of fat and of calcium in the diet.

Case 5. All the features associated with the variations made in the calcium of the intake in the previous experiments are reproduced in Case 5. In Period II diluted whey was substituted for unmodified milk, so that both the fat and calcium of the intake were very considerably reduced. The fall in faecal weight and the corresponding diminution of the quantity of calcium soaps in the faeces are in consequence very pronounced.

In Period III the addition of a large excess of CaO to the diet is seen to have had no appreciable effect on the faecal weight. There is a striking fall in the percentage of combined fatty acids, evidently due to the low fat content of the whey. The greater part of the calcium was shown to have been excreted as a carbonate in the faeces (p. 52).

The fat content of the diet was then increased by the addition of milk fat to the whey, the calcium content remaining unaltered. The distribution of the fat in Period IV shows that a prompt increase in calcium soap formation had

occurred, the percentage of combined fatty acids in the faeces being more than three times that of the preceding period. The rise in the faecal weight, the percentage of total fatty derivatives, and the amount of calcium soaps excreted are evident.

The addition of acid sodium phosphate to the diet (Period V) made no appreciable difference in the average daily faecal weight, and the extent to which calcium soap formation proceeded remained practically unaltered.

Case 6. The last experiment of the series was designed to ascertain the effects of calcium added to the diet, when all the other constituents were unaltered. In the second period, 1 grm. CaO as calcium lactate was added daily to the unmodified milk diet of Period I. Adequate amounts of fat and phosphorus were therefore present, though calcium was in excess. No appreciable change in the distribution of the fatty derivatives resulted. The total amount of calcium soaps excreted, however, was increased, and there was a very pronounced rise in the average daily weight of dried faeces. These results serve to corroborate the findings of the previous experiments in which reductions in the amount of calcium ingested are made.

Discussion. Holt, Courtney, and Fales (2), who examined the fat distribution in the stools of a large number of infants, found that on a diet of cow's milk the average percentage of fat of the faecal solids was 36.2. Hutchison (8), working on fat absorption in children, showed that the total fatty derivatives generally formed about one-third of the dried faeces. In the first period of each experiment the total fat of the faeces was generally above the normal, and in Case 3 very considerably higher. The relation between an excess of fat in the stools and the mode of elimination of calcium and phosphorus is discussed later.

When diarrhoea ensued, the distribution of the fatty derivatives was completely changed. There was an excessive loss of neutral fat and free fatty acids. In all cases this change in the nature of the faeces was coincident with an extreme reduction in the calcium of the intake, to which must be attributed the smaller amount of calcium soaps in the faecal solids. Holt *et al.* (2), in their studies on fat excretion, constantly found a diminished percentage of calcium soaps in diarrhoeal stools. They also showed that the addition of calcium carbonate to the diet in diarrhoea led to an increased formation of calcium soaps, an observation which receives corroboration from the result of the three last experiments of the series. In one of these (Case 3) the addition of a small quantity of calcium to the diet was followed by an appreciable increase in the percentage of calcium soaps in the faeces. The alteration in the physical state of the stools is interesting in view of this chemical change. These became white and semi-solid, and diarrhoea immediately ceased, an occurrence which suggests that calcium soaps may play an important part mechanically in controlling excretion by the bowel. According to Bosworth, Bowditch, and Giblin (1) the presence of an excess of calcium soaps in the intestine may be the cause of severe constipation in young infants fed on unmodified cow's milk. These observers have demonstrated the insolubility of calcium salts of the higher fatty acids in the intestinal juices, and hold that neutral fat and free fatty acids are incorporated in the mass of insoluble soaps formed in the intestine. There is therefore an undue loss of fatty derivatives in the stools from diminished

absorption, in addition to the deleterious effects produced by constipation. Their conclusions as to the mechanical action of calcium soaps receive considerable support from the results recorded. In the second period of the experiments, when the intake of milk solids was halved, there was a corresponding fall in the faecal weight and the amount of calcium soaps excreted, and the composition of the faeces with respect to fatty derivatives approximated to the normal. Again, the ingestion of an excess of calcium in the absence of an adequate amount of fat in the diet had no effect on the faecal weight (Case 5), since the formation of calcium soaps could not take place, while the addition of calcium to a diet rich in fat was immediately followed by an increased excretion of insoluble soaps and consequently of faecal solids.

These results also show that the percentage of fatty derivatives in the faeces depends on the quantity of fat ingested when this is beyond certain limits, but that their excretion is largely influenced by the degree to which calcium soap formation in the intestine proceeds.

With regard to the influence of calcium soap formation on faecal weight, it will be observed that this is not due to the weight of the soaps themselves, but apparently to the property which they possess of incorporating or occluding the other constituents of the intestinal contents in amount proportional to their mass. In this respect calcium soaps may be regarded as the basis of faeces formation. On a diet of cow's milk the composition of the dried faeces is approximately constant for the same individual, and within limits independent of the amount ingested. This fact may be explained on the assumption that the calcium soaps formed in the gut incorporate a proportional amount of the intestinal contents, the latter being derived chiefly from the milk solids, in which the mineral elements and the fat bear a constant relation to each other.

(d) *The relation of phosphorus to fat excretion.* Cow's milk contains an excess of phosphorus over the equivalent amount required to form tri-calcium phosphate with all the available calcium, a condition possibly correlated with the requirements of the growing tissues other than bone, in the building up of phospho-lipoids, nucleic acid, and other organic compounds of phosphorus.

In contrast to calcium, the excretion of phosphorus in the urine is considerable, though generally less than the phosphorus excreted by the bowel in combination with calcium, in the case of healthy infants on a diet of unmodified cow's milk. The greater part of the total calcium eliminated in the faeces is in combination with phosphoric acid, the remainder being in the form of insoluble soaps (p. 46). It was therefore of interest to follow the excretion of phosphoric acid in relation to that of fat when the derivatives of the latter in the faecal solids were found to vary.

Method: The mode of elimination of phosphorus in normal subjects was compared with that in a series of cases in which the excretion of fatty derivatives was excessive, the diet in all cases being unmodified cow's milk. The data were obtained as before by estimations of CaO and P_2O_5 in the separated urine and dried faeces. The results are arranged in Tables IV and V.

TABLE IV

Comparison of Excretion of Phosphorus by Urine and Faeces.

Diet: Unmodified Cow's Milk.				
	Case 1.	Case 2.	Case 3.	Case 4.
Period of observation	5 days.	5 days.	4 days.	5 days.
P ₂ O ₅ in urine	39.3 %	37.0 %	40.4 %	32 %
P ₂ O ₅ in faeces	60.7 %	63.0 %	59.6 %	68 %

Ratio of CaO to P ₂ O ₅ in Dried Faeces.				
	Case 1.	Case 2.	Case 3.	Case 4.
Period of observation	5 days.	4 days.	6 days.	5 days.
CaO to P ₂ O ₅	1.27	1.4	1.3	1.35
CaO %	9.86	9.8	8.62	7.8
P ₂ O ₅ %	7.72	6.9	6.44	5.75

Results: The ratio of CaO to P₂O₅ in the normal dried faeces, which contained approximately 30 per cent. of total fat, was relatively constant and gave an average of 1.3. This result is in agreement with the observation of Von Wendt, quoted by Keith and Forbes (6), that the greater part of the calcium in the faecal solids exists as tri-calcium phosphate. The ratios found in normal dried faeces are slightly higher than the ratio of CaO to P₂O₅ in the latter salt (1.18), since a small proportion, generally about one-fifth of the total calcium, is in combination with fatty acids as insoluble soaps (6).

Of the total phosphoric acid eliminated 30 per cent. to 40 per cent. appeared in the urine, the greater part of the phosphorus having been excreted in combination with calcium in the faeces. The absorption of phosphorus is therefore considerably in excess of the amount retained.

The distribution of phosphoric acid in the urine and faeces, when the fat content of the latter was abnormally high, is shown in Table V.

TABLE V

Distribution of Fat and Phosphoric Acid.

Diet: Unmodified Cow's Milk.								
No.	Duration of Observation.	Neutral Fat.	Free Fatty Acids.	Combined Fatty Acids.	Total Fatty Acids.	Total Fat.	CaO to P ₂ O ₅ faeces.	% P ₂ O ₅ urine. % P ₂ O ₅ faeces.
1. Rickets	4 days	4.17	22.5	13.0	35.5	39.67	1.58	46.6 53.4
2. Rickets	4 days	6.57	17.58	17.10	34.68	41.25	1.31	49.8 50.2
3. Fat dyspepsia	4 days	2.13	17.62	31.20	48.82	50.95	1.8	55.3 44.7
4. Marasmus	1 day	9.89	18.61	40.9	59.51	69.4	2.1	—
5. Congenital obliteration of the bile ducts	4 days	13.18	34.92	27.67	62.59	75.77	3.06	74.4 25.6

These results show that an increase in the percentage of fatty derivatives is associated with an increased amount of phosphoric acid in the urine and a diminution in the faeces. Consequently the ratio of CaO to P_2O_5 in the faecal solids is high (cf. Table IV). With the exception of the second case, these ratios form an ascending series corresponding to the increasing percentages of fatty derivatives in the dried faeces. A correlated deflexion of phosphoric acid from the faeces to the urine is also indicated. In Case 4 the urine could not be collected quantitatively, but the high ratio of CaO to P_2O_5 in the faeces show that the urinary phosphorus must have been considerably greater than the normal.

The chief conclusion to be drawn from these results is that the extent of the deviation of phosphorus from the intestinal route of excretion to the urine is dependent on the amount of free fatty acids which persists in the gut contents.

It has been shown that an excess of fatty derivatives in the stools is associated with an unduly large formation of calcium soaps (Table III). The explanation of the partial deviation of phosphoric acid from the faeces to the urine would therefore appear to be that the normal restriction of phosphoric acid to the gut in the form of insoluble phosphate of lime is interfered with to an extent which is relative to the concentration of fatty acids in the intestinal contents. It has been shown that the opposite effect can be produced experimentally (pp. 52 and 53) by adding an excess of calcium salt to a diet containing a relatively small amount of fat. According to Bosworth *et al.*, the phosphoric acid existing as CaHPO_4 in milk is restricted to the intestine and appears as such in the faeces. The phosphorus combined in the casein is excreted by the urine. The latter can be rendered phosphorus free by feeding on calcium caseinate and calcium acetate.

A point of practical interest is the nature of the faeces, which are associated with this alteration in the mode of phosphorus excretion. The stools, since they contain an excess of calcium soaps, are bulky, and the average daily weight of dried faeces is high. The increased excretion of fatty derivatives leads to a diminished concentration of mineral matter, which in normal infants on a milk diet is about 22 per cent. of the dried faecal weight. The percentages of CaO and P_2O_5 found in the dried faeces are consequently very low (*v.* Table II). The stools are generally white and of a pasty consistency, and may actually melt in the process of drying on a water-bath. On ignition the dried faeces burn with a smoky, luminous flame, leaving a flaky scattered ash consisting chiefly of calcium carbonate in contradistinction to the compact ash of normal faeces, in which the lime is almost wholly in combination with phosphoric acid.

The series of cases under discussion is also of interest from the clinical point of view, since the presence of an excess of fatty derivatives in the faeces of infants fed on unmodified cow's milk is so frequently encountered. In Case 6 (congenital obliteration of the bile ducts) there was a very large excess of fatty acids in the faeces, a condition due to non-absorption of digested fat and invariably associated with the absence of bile from the gut (6). Jaundice was never present at

any time in the other cases of the series. The excess of fatty derivatives in the faeces and the deflexion of phosphorus from the faeces to the urine suggest, however, that in these hepatic insufficiency, varying in degree, may have been a feature common to all. According to Brodin (9) there may be severe functional insufficiency of the liver, characterized by a retention of bile in the blood without the appearance of jaundice. Since, as has been demonstrated, the excretion of calcium, phosphorus, and fats are so closely interdependent, attention might be profitably directed to the study of the liver functions in connexion with the absorption and retention of the mineral elements, and especially in diseases of infants such as rickets and fat intolerance, in which the aetiology is still obscure.

Summary. 1. The excretion of calcium, phosphorus, and fatty derivatives are interdependent, calcium being eliminated chiefly as phosphate and to a lesser extent as insoluble soaps, the relative amounts of these varying with the conditions of the intestinal contents.

2. 20 to 30 per cent. of the total CaO excreted normally exists in the form of calcium soaps.

3. A large proportion of the ingested calcium and phosphorus is restricted to the gut, and appears in the faeces as tri-calcium phosphate. Consequently the absorption of a considerable part of the intakes of these is normally prevented.

4. The total amount of calcium and phosphorus eliminated is nearly proportional to the intake. No evidence was obtained that mineral matter from endogenous sources was excreted in the faeces to any appreciable extent.

5. The urinary calcium is a very small fraction of the total calcium excreted. It is slightly increased by an increased intake of calcium salts, by the administration of acids salts, and, generally, by acid formation in the intestine.

6. In normal infants 40 per cent. of the total phosphorus excreted appeared in the urine, 60 per cent. in the faeces. With acid formation in the intestine, less phosphorus is excreted by the faeces, more by the urine. It was found that the degree of deviation of phosphorus to the urine was roughly proportional to the amount of fatty acids in the faeces, and consequently to the extent to which fatty acids had displaced phosphoric acid from its normal combination with calcium in the intestine.

7. It is argued that the phosphorus which is excreted by the faeces has been in greater part restricted to the intestine owing to the presence of calcium salts, and cannot be regarded as a re-excretion into the intestine. The excess of phosphorus over the equivalent amount of calcium forming tri-calcium phosphate is absorbed, and a part of this is retained, the remainder being excreted in the urine.

8. An excess of calcium salts restricts an increased quantity of phosphorus to the intestine. In a particular case, in which the intakes of fat and phosphorus were low, an excess of calcium in the diet rendered the urine phosphorus free.

9. With a persistent excess of fatty acids in the intestine a much greater proportion of calcium is excreted as soaps.

10. The influence of calcium soaps in controlling the bulk of faeces is discussed. The average daily faecal weight is shown to depend chiefly on the degree to which calcium soap formation proceeds. The calcium soaps act mechanically by incorporating in their mass fatty derivatives, the mineral residues of the diet, and the unabsorbed intestinal secretions, and consequently are regarded as the basis of faeces formation. The faecal solids of infants are shown to be derived in large part from the diet.

11. When both fat and phosphorus are very deficient in the diet, an excess of calcium in the intake may be excreted as carbonate.

12. No evidence of absorption of calcium in excess of requirements with subsequent re-excretion into the bowel was obtained. On the other hand, all the observations made seemed to indicate that the greater part of the calcium in the intake is restricted to the gut; and, except the small amount excreted in the urine, the amount absorbed is nearly equivalent to the amount retained.

13. The excretion of calcium and phosphorus in relation to fats is discussed in certain pathological cases, in which an excessive soap formation was a feature common to all. It is suggested that in these the common causative factor was a persistence of free fatty acids in the intestine, possibly secondary to some degree of hepatic insufficiency.

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STUDIES ON CALCIUM AND PHOSPHORUS METABOLISM

PART II. THE METABOLISM OF CALCIUM AND PHOSPHORUS IN RICKETS

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A CONSIDERABLE amount of research work has been recently undertaken, particularly in this country and in America, on the pathological processes which are involved in the softening of the bones in rickets. It has long been recognized that whatever the causation of rickets may be, a serious defect in the metabolism of the inorganic constituents of bone must necessarily exist, and this outstanding characteristic of the disease has served to direct attention perhaps too exclusively to the study of calcium. It has been shown by the earlier workers on this subject that the defect of mineral matter may be extreme.

A series of examinations of rachitic pups used in experimental studies of the disease showed that the mineral matter of the dried limb bones was as low as 17.7 per cent., the average amount for normal animals of the same age and breed being 44.9 per cent.

The possible cause of such a deficiency of mineral matter has been the subject of much speculation, but so far the results of published work have not furnished any explanation of the condition.

When a chemical examination of the ash of rachitic bones is made it is found that the ratio of CaO to P_2O_5 , even in the most pronounced cases of the disease, does not differ appreciably from that of normal bone.

In the case of the animals referred to above this ratio was found to be 1.2:1. A series of examinations of the femora of infants, both rachitic and normal, gave the value 1.35:1.

On account of this constancy of CaO and P_2O_5 in bone ash, Gassman (1) and others have suggested structural formulae to represent the lime-phosphoric acid combination which comprises nearly the whole of the inorganic matter. Gassman also noted the similarity in the compositions of the ash of normal and rachitic bones. It would therefore seem that the bone 'softening' in rickets involves a defect in phosphorus metabolism as important as that of calcium. The metabolic study of both of these elements was consequently undertaken.

As pointed out by Findlay, Noel Paton, and Sharpe (2) in a previous paper in this *Journal* in which calcium metabolism alone was considered, the lack of inorganic matter in normal amount in the rachitic bone may result in two possible ways:

(1) A decalcification of the osseous tissue normally formed—a 'solution' of bone.

(2) A defective ossification associated with either—

(a) deficient absorption of these elements from the digestive tract, or

(b) defective utilization of normally absorbed calcium and phosphorus.

In 1911 Schabad (3) published results of metabolic studies in rickets which seemed to show that decalcification was the cause of bone softening. He arrived at this conclusion on finding negative retentions of calcium and phosphorus among certain of his cases of rickets, the output of these elements in the excreta being greater than the amounts ingested. He also concluded that an excessive excretion of both elements, but particularly of the phosphorus, occurred in the faeces. It was obviously of importance to reinvestigate these results in order to ascertain if any actual loss of mineral matter from formed bone took place during the course of the disease. Findlay, Noel Paton, and Sharpe (*loc. cit.*) give a complete summary of the methods of investigation and the conclusions of various workers in this field, and a further discussion of the theories advanced with regard to the aetiology of rickets need not be entered into here.

From their own results these workers formed the opinion that the deficiency of mineral matter in the rachitic bone was not due to excessive decalcification. On the other hand, they were unable to determine definitely whether rachitic 'softening' was dependent on a failure of supply of calcium to the bone or not, since they found no differences in the calcium content of the blood of normal and rachitic subjects; that is, neither the defect of faulty transport of calcium to the growing bone, nor that of assimilation of the bone-forming elements at the ossifying centres, was excluded as a factor in the softening process. They argued that a defect in the absorption of calcium from the intestinal tract was probably not a causative factor. The older theory, that rickets was caused by a deficiency in the amount of calcium in the diet, is no longer tenable in the light of the experimental work of Noel Paton, Findlay, and Sharpe, and from the studies of dietaries in rachitic families.

Present Investigation. The importance of securing subjects suffering from the disease in its active stages has been demonstrated by Findlay, Noel Paton, and Sharpe (2). Cases of early rickets in infants were therefore selected. Balance experiments were conducted on these and on normal infants of approximately the same age. Each subject was placed on a 'metabolism' bed devised by Findlay (2), whereby the excreta would be collected quantitatively and separately. In female infants the mixed urine and faeces were evaporated to dryness on a water-bath, then weighed, finely ground, and preserved in air-tight bottles for examination. The estimations of CaO and P_2O_5 in the excreta were made by the usual

gravimetric methods. In the later experiments these estimations were carried out on samples of the combined urine and faeces, representing the excreta collected during the whole period of observation, and the daily estimations of CaO and P_2O_5 in the excreta were discontinued. The diet in all cases consisted of undiluted cow's milk, sweetened with cane sugar, and given in accurately measured quantities. Samples of the feeds were taken daily for the estimations of CaO and P_2O_5 , so that the total amounts of the mineral matter ingested during the period of observation could be determined. It is perhaps noteworthy that while the variations found in the calcium and phosphorus contents of the many specimens of cow's milk examined were small (CaO 0.155 per cent.—0.19 per cent., P_2O_5 0.20 per cent.—0.23 per cent.) these variations were of decided importance with regard to accuracy when the period of observation was of some length. The fallacies inherent in metabolic studies of short duration have been pointed out by Findlay, Noel Paton, and Sharpe (*loc. cit.*).

Each experiment was continued for a period of not less than five days in the present series of observations. During a pre-period of at least three days the subject was fed on the same quantity of milk daily as in the experimental period to ensure metabolic equilibrium.

Park and Howland (4) have raised certain objections to this method of investigation. They regard the period of observation, necessarily limited to several days, as being so short relatively to the duration of the illness that the retentions of CaO and P_2O_5 estimated cannot afford an index of mineral metabolism during the lengthy course of the disease. They also consider that the excreta, especially the faeces, do not correspond to the period of intake. Both of these objections apply to balance experiments conducted over periods of short duration, and were recognized early in the course of this work. Theoretically the retentions of CaO and P_2O_5 ought to be determined at intervals during the course of the illness in order to follow more accurately the fluctuations of the perverted mineral metabolism. Orgler (5) indeed holds the view that there are alternating periods of regression and progression in the pathological processes which characterize the disease, and Schabad's results show increased retentions of CaO and P_2O_5 during the period of recovery.

An attempt was made at first to repeat balance experiments on a number of young rachitic infants at monthly intervals from the time when the first definite signs of the disease were manifest, but had to be abandoned from various causes. It was finally considered that if the examinations were made on young subjects who had been under supervision for some time, and in whom clinical signs were pronounced and the bone changes progressive, the danger of estimating the retentions during a quiescent period of the disease would be minimized. The method as carried out is of undoubted value for the purpose of comparing the retentions of normal and rachitic children. If the period of observation, including the pre-period, is not less than ten days, a fairly close correspondence between intake and excretion may be established, and any large deviation from uniformity in faecal excretion during such a period

can be recognized by weighing the dried faeces daily. The accuracy of balance experiments depends largely on the length of time over which they can be conducted.

A serious obstacle to accuracy in the method of investigation is the number of practical difficulties encountered. The feeding of infants with measured quantities of milk over an extended period requires considerable care to ensure accuracy of intake. The onset of vomiting which is always to be feared, even in healthy subjects, is sufficient to destroy the quantitative value of the experiment, since the loss in the calculated intake cannot be estimated. A large number of observations, some of them extending over a week, had to be discarded on account of this accident. The results of a number of examinations of supposedly normal infants had also to be rejected on the ground that the faeces were abnormal in composition. Generally this abnormality was an excess of fatty derivatives in the stools. It has been shown (Part-I) that the mode of excretion of both CaO and P_2O_5 is dependent on fat excretion. When fatty derivatives are in excess in the stools there is a considerable deviation of P_2O_5 from the intestinal contents to the urine in excretion, while an unduly large part of the calcium is linked to fatty acids as soaps. Though the relation of an excess of fat in the stools to the retention of mineral matter is as yet unknown, dried faeces containing over 40 per cent. of fatty derivatives were regarded as abnormal in this investigation. Unfortunately it is impossible to determine with any degree of certainty if faeces are normal in uniformity of bulk or in composition by naked-eye examination alone. They must be collected, dried, and examined quantitatively. This procedure involves a considerable amount of time.

The results given in the table on p. 67 were obtained from observations upon cases in which the course of each experiment was free from error due to any of the causes described above.

Discussion. In the normal series there is a well-marked retention of both CaO and P_2O_5 . The retentions of CaO and P_2O_5 per kilo per day are approximately equal except in the last case (A. Q.), where the phosphoric acid retained was less than the lime. The faeces of this subject contained a somewhat high fat content, and perhaps the case should not be included in the normal series.

Since about 90 per cent. of the two elements retained is required by the rapidly growing skeleton, and the ratio of CaO to P_2O_5 in human bone is 1.3 : 1 (approx.), it is evident that an excess of phosphorus is retained over the theoretical amount required for ossification. It is noteworthy that this excess of P_2O_5 over CaO is provided naturally in milk, and is probably related to the requirements of the growing soft tissues for phospho-lipoids, nucleic acid, and other organic phosphorus compounds.

The amounts retained per kilo of body-weight are variable, as was to be expected. In the rachitic series the retentions of CaO and P_2O_5 are much less than the lowest normal retention, with the exception of Cases 2 and 3. The first of these (S. W.) was regarded as a mild example of the disease, the signs of

Normal Subjects.

Case.	Age.	Weight (kilos).	Period. (days).	Intake (daily).	Excretion (daily).	Percentage Retention of Intake.	Retention per kilo per day.
				CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .
1. J. W.	1 year	7.6	6	3.108 3.793	2.236 2.983	28.0 22.0	0.124 0.123
2. A. S.	1 $\frac{1}{2}$ "	6.1	7	1.65 2.2	1.255 1.798	24.0 18.0	0.064 0.065
3. A. P.	1 $\frac{1}{2}$ "	6.0	4	1.55 2.2	1.217 1.867	21.0 15.0	0.055 0.055
4. A. Q.	1 $\frac{1}{2}$ "	6.3	4	1.85 2.25	1.222 1.87	34.0 17.0	0.098 0.06

Rachitic Subjects.

Case.	Age.	Weight (kilos).	Period (days).	Intake (daily).	Excretion (daily).	Percentage Retention of Intake.	Retention per kilo per day.	Remarks.
				CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .	CaO. P ₂ O ₅ .	
1. J. H.	1 $\frac{1}{2}$ years	7.6	6	1.83 2.41	1.704 2.408	7.0 Nil	0.016 Nil	Extreme rachitic changes. Unable to stand supported
2. S. W.	1 $\frac{3}{4}$ "	5.55	7	1.71 2.355	1.317 1.91	23.0 19.0	0.07 0.08	Rachitic changes slight. Can stand with support.
3. J. T.	1 $\frac{1}{2}$ "	6.4	6	1.525 2.068	1.185 1.65	22.0 20.0	0.053 0.065	Bones poorly calcified and show pronounced rachitic changes. Unable to stand supported
4. E. F.	1 $\frac{1}{2}$ "	4.62	5	1.422 1.934	1.178 1.812	17.0 6.05	0.052 0.020	Epiphyseal enlargement at wrists and rachitic rosary.
5. O. M.	1 $\frac{1}{2}$ "	8.8	8	1.851 2.387	1.593 2.216	14.0 7.01	0.029 0.019	All other children of family rachitic
6. T. S.	1 $\frac{1}{2}$ "	5.8	5	1.264 1.505	1.146 1.418	9.0 6.0	0.02 0.015	Extreme rachitic changes. Cannot sit or stand
7. A. G.	1 $\frac{1}{2}$ "	6.45	7	1.462 2.00	1.524 1.895	6.0 5.0	0.014 0.016	No signs of rickets till age of 9 months. Epiphyseal enlargements at wrist Slight rachitic changes seen on X-ray examination at age of 8 months

rarefaction at the epiphyseal ends of the radius and ulna found on X-ray examination being much less evident than in the others. No explanation for the comparatively high retentions obtained in the second (J. T.) was apparent. In this case the bony changes were very definite. Whether the disease was active at the time when the metabolic experiment was conducted or had passed into a quiescent or healing stage could not be determined.

Case 6 is of special interest. The infant (T. S.) was considered after careful clinical and X-ray examination to be normal, and was selected for observation in a control experiment. The results recorded in the tables showed such low values for the retentions CaO and P_2O_5 that considerable doubt was felt regarding the inclusion of these in a normal series. The distribution of CaO and P_2O_5 and that of fatty derivatives which were determined from a detailed analysis of the faeces showed that the latter were normal in composition.

Three months later, this infant, which had in the interval been sent home, was again examined in hospital. Definite signs of rickets were seen to have developed, and X-ray examination showed defects in ossification of the radius and ulna.

The history of Case 7 (A. G.) is somewhat similar. The subject showed no rachitic changes, and appeared to be in normal health when the balance experiment was made. The percentages of CaO and P_2O_5 in the faecal solids were high, while the retentions were excessively low for a normal infant. Definite signs of rickets were evident three months later.

It is not improbable that the retention values in these two cases were determined at a time when the disease was progressive, but before signs of defective ossification were evident. A similar case is recorded by Findlay, Noel Paton, and Sharpe (*loc. cit.*).

It will be observed that in the rachitic series the retentions of P_2O_5 are generally less than those of CaO . The defect in the metabolism of phosphorus would therefore appear to be even greater than that of calcium. This feature of mineral metabolism in rickets was noted by Schabad, who came to the conclusion that there was an excessive loss of P_2O_5 from involvement of the soft tissues rich in phosphorus, as well as a loss from depletion of bone salts.

With regard to calcium, these results are in agreement with those of Findlay, Noel Paton, and Sharpe (2), Holt, Courtney, and Fales (6), and many continental workers.

No negative retentions of CaO and P_2O_5 were found in any of the rachitic subjects, though in Case 1 (J. H.) there was no retention of P_2O_5 . The bone-forming elements were generally being retained, and therefore ossification must have been merely reduced in activity, at least during the period of observation in all the cases of rickets examined with the possible exception of the first.

It is clear that if negative retentions were a feature of the active stage of disease, as Schabad concluded, excessive decalcification of bone would have to be accepted as the causal factor in the process of softening. No support for this argument is contained in the above results. Findlay, Noel Paton, and

Sharpe have suggested that softening might be due to a failure of the growing bone to fix the calcium which is liberated by the normal resorption of formed osseous tissue during extension of the process of ossification. But in that case also there would be a loss of mineral elements from the body and negative retentions in balance experiments invariably found. Otherwise the liberated calcium and phosphorus would become concentrated in the soft tissues, or increased in the blood. These workers found the same concentrations of calcium in the muscle, brain, and blood of rachitic pups as in the soft tissues of normal animals.

In the absence of definite evidence of excessive decalcification in rickets, two possible explanations for the diminished retentions of the bone-forming elements still remain:

(a) There may be an absorption of adequate amounts of CaO and P_2O_5 from the intestinal tract, but failure of utilization of these at the centres of ossification. The re-excretion of the greater part of the normally absorbed mineral elements which would follow failure of fixation of these by the growing bone would result in diminished, but not necessarily negative, retentions of the two elements. Essentially such a condition would simply be one of defective ossification. Calcification would not keep pace with the growth and elaboration of the tissue framework which precedes normal ossification, and a relative softening would result. A theoretical objection to this explanation is that there would probably exist a calcium and a phosphorus content of the blood at higher levels than in the normal subject, and as far as has been ascertained no increase of the two elements in the blood of rachitic subjects has been demonstrated. Howland and Krammer (7) found the inorganic phosphate of the blood reduced in rachitic children. Caution must be exercised, however, in drawing conclusions from the results of blood examinations alone. There is considerable variation in technique and in the published results of different workers in this field of research. When the chronic nature of the disease and its ill-defined course are considered, it is conceivable that comparatively small aberrations in the metabolism of one or other of the bone-forming elements, which would not be revealed by estimations of these in the blood, might still lead to gross defects in ossification. Calcium estimations made on blood drawn from the peripheral circulation cannot be regarded as affording an index of the amount of calcium absorbed from the intestine. Normally this amount is often only a comparatively small proportion of the intake. It may be rapidly removed from the blood-stream by diffusion and deposition.

(b) The remaining possible explanation of the diminished retentions in rickets is simply that there is initially a defective absorption of calcium from the intestine. In view of the widespread prevalence of gastro-intestinal disorders in infants, and the sensitiveness of the digestive apparatus in the early period of life to comparatively trivial defects of diet, it has perhaps an additional interest. The results obtained in treating the disease dietetically by the administration of cod-liver oil (4), as well as those of investigators who have

induced rickets experimentally in rats by altering the diet, also seem to suggest the possibility of an alimentary defect being associated with the disease. According to Shipley *et al.* (8), the phosphate ion in the diet may possess a determining influence for or against the development of rickets in rats. The association of a catarrhal condition of the small intestine with an outbreak of rickets among foxhound puppies was noted by Bull (9), who formed the opinion that the bone changes were secondary to the absorption of toxins from the intestine. This observer also considered that diet was an important factor in the aetiology of the disease.

No differences in result can be attributed to the diet used in the experiments recorded here as regards the quantity or the nature of the combinations of the lime and phosphoric acid in the food. These were identical in the two series discussed, as they probably are in the infant diets of the poor, whether in rachitic or normal families. The diminished retentions found did not depend therefore on a diminished absorption caused by an insufficiency of calcium and phosphorus supply.

Unfortunately our present knowledge of the mode of absorption and the conditions of transport to the ossifying centres of the two elements is very incomplete, and we do not know the relationship which holds between their retention and absorption. It has long been supposed, chiefly from the experimental results of work on animals (10), that calcium is first absorbed from the intestine, then re-excreted into the large bowel. Recently the experiments of Grosser (11), who found increased excretion of calcium in the faeces after intravenous injection of soluble calcium salts, have been held to confirm this supposition. As meconium and the intestinal secretions do contain both calcium and phosphorus in small amounts the excretion of these elements into the intestine is certainly possible. But with regard to infants fed on a milk diet it does not seem to be established that the re-excretion into the intestine of any large part of the calcium and phosphorus absorbed during digestion takes place normally. The excretion of these elements in infants has been studied concurrently with metabolism in rickets, and is discussed in the previous communication (Part I). The results obtained from experiments on dogs and from observations on children do not give support to the view that, at least on a milk diet, a large excess of CaO above requirements is absorbed from the intestinal tract and re-excreted into the bowel; but they appear to indicate that most, if not all, of the mineral matter which appears in the faeces is an unabsorbed residue of ingested calcium and phosphorus.

On account of this lack of precise knowledge concerning the normal absorption and excretion of calcium and phosphorus, the definite conclusion that diminished absorption of calcium is not the cause of the diminished retentions in rickets would appear to be unwarranted.

The more markedly diminished retentions of P_2O_5 found in the rachitic cases as compared with those of CaO are possibly significant.

In the studies made on the excretion of calcium and phosphorus (Part I) it

was shown that an excess of phosphorus above requirements is absorbed, since the greater part of the urinary phosphorus is derived from the intake. Further, an excess of calcium in the intestine (p. 53) is associated with a diminished urinary elimination of phosphorus, the latter tending to be restricted to the gut as insoluble phosphate of lime. A deficient absorption of calcium from the intestine is therefore compatible with diminished excretion of phosphorus by the urine and an increased excretion by the faeces.

Since most of the calcium and the greater part of the phosphorus retained are required in the elaboration of bone, it is conceivable that the diminished retention of phosphorus found in rickets is due, not to diminished absorption, but to diminished fixation by the calcium. In this connexion the following feeding experiment on dogs is of interest.

The retentions of CaO and P_2O_5 were determined on two pairs of animals of the same age and litter. The diets, which were poor in calcium, but adequate in every other respect, were identical in composition and quantity in the two pairs, except that to one (No. 2) an excess of calcium lactate was added.

The following result was obtained:

	No. 1 (Ca-poor diet).		No. 2 (Ca-excess diet).	
	CaO	P_2O_5	CaO	P_2O_5
Intake per day	0.184 grm.	1.162	1.425	1.162
Retention per kilo per day	0.016 grm.	0.005	0.127	0.086

These show that a small retention of CaO was associated with a small retention of P_2O_5 (No. 1). When the retention of calcium was increased by the addition of calcium lactate, there was a correspondingly large increase in the amount of phosphorus retained (No. 2). It would appear as if the fixation of P_2O_5 in these cases had been determined by the amount of CaO retained, since in both an excess of P_2O_5 above requirements had been absorbed and eliminated in the urine. The animals were maintained on the respective diets for a period of three months. Post-mortem examination then showed that ossification of the skeleton of the dogs on the Ca-rich diet was considerably in advance of that of the animals on the Ca-poor diet. The bones were thicker and heavier, and the total skeleton contained a much greater quantity of mineral matter. No very marked differences were found in the calcium and phosphorus contents of the soft tissues. In this experiment the increased retention of calcium had therefore resulted in an increased fixation of phosphorus by the growing skeleton.

An important aetiological consideration of the disease arises immediately if this view be accepted. Since diminished absorption of calcium cannot as yet be excluded as a factor in the causation of 'softening' of the bone in rickets, the integrity of the gastro-intestinal functions in the rachitic subject ought still to be regarded as doubtful, and further work directed to the study of the absorption of mineral matter from the intestinal tract and its utilization in the normal and rachitic subject.

Summary. 1. In normal infants on a diet of cow's milk the retentions of

CaO and P_2O_5 estimated from balance experiments were found to be approximately equal.

2. An excess of P_2O_5 is retained over the equivalent amount of CaO required for bone formation.

3. In the cases of rickets examined there were diminished retentions of CaO and P_2O_5 , the defect in the latter being the more pronounced.

4. It is suggested that the diminished retentions of P_2O_5 were not due to a lessened absorption of phosphorus, but to a diminished fixation by the calcium, the absorption of the latter being defective.

5. No negative retentions of CaO or P_2O_5 were found; and consequently no support for the theory that excessive decalcification is the cause of bone softening in rickets was obtained.

6. The causes which might give rise to diminished retentions of the bone-forming elements are discussed. It is argued that defective absorption of calcium from the intestine, possibly the result of some alteration in the gastrointestinal functions, cannot yet be excluded as a factor in the causation of bone 'softening' in rickets.

This work was carried out in connexion with the Child Life Investigation of the Medical Research Council. I desire to express my indebtedness to Prof. D. Noel Paton for much helpful advice and criticism, and to Dr. Findlay for the use of cases in the Royal Hospital for Sick Children.

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A STUDY OF ORTHOSTATIC ALBUMINURIA BY MEANS OF GRAPHIC RECORDS¹

By JAMES W. RUSSELL

Introduction.

IN this paper I have endeavoured to make a more or less continuous study of the urine secretion and albumin output in such apparent cases of orthostatic albuminuria as I have been able to observe in hospital, and to compare the behaviour of the cases in those respects with that observed in certain cases of mild nephritis occurring in children.

At the outset of my study I was pulled up by the absence of any known method for the rapid clinical estimation of albuminuria of small degree. Many of the urines that I was dealing with contained an amount of albumin far below the limit of measurement possible by the Esbach albuminometer, and the record of 'light clouds', 'hazes', and 'faint hazes' was of no use for my purpose. Even when the albumin was measurable by the Esbach method, the measurements did not attain the degree of delicacy that I needed. I therefore found myself in the position of having to devise some rapid and reasonably accurate method for the estimation of albumin in both small and large amount, or of abandoning my study.

I do not consider the method that I have to describe as anything more than a means for obtaining for clinical purposes an approximately correct comparative estimation of the amounts of albumin passed from hour to hour. Like most of our clinical quantitative methods, it does not claim to attain strict scientific accuracy, but by its use I have been enabled to obtain what I believe to be essentially true graphic records of the output of albumin, from which I think that something is to be learnt.

The method is essentially that of the Gowers haemoglobinometer, substituting for the standard tinted jelly a fluid containing a standard haze. The albumin to be estimated is coagulated, and the number of dilutions needed in order to match the standard gives a measure of the amount of albumin contained. The tubes are flat-bottomed tubes, made of thin glass, 15 cm. in length, with an internal bore of 1.1 cm. They are made for me by Messrs. Philip Harris & Co., of Birmingham.

¹ Based upon the Ingleby Lectures delivered in the University of Birmingham on May 17 and 24, 1922.

The standard haze which I have found most convenient for my purpose is obtained from three stock solutions, and is made up afresh for each day's estimations:

1. $\frac{N}{500}$ barium chloride solution in distilled water (0.02443 per cent.).
2. $\frac{N}{500}$ magnesium sulphate solution in distilled water (0.02467 per cent.).

3. Distilled water, to every 100 c.c. of which are added 0.04 c.c. of saturated aqueous picric acid solution, and 0.02 c.c. of freshly made 0.2 per cent. Bismarck brown,² two pigments that together imitate very closely the colour of a pale urine. I owe to Dr. Hillier, Clinical Pathologist to the Birmingham General Hospital, the suggestion of this dye. A crystal of thymol is added to each of the first two solutions.

To make the haze, half a cubic centimetre each of solutions 1 and 2 are mixed together in one of the tubes, and allowed to stand for exactly five minutes. 5 c.c. of the pigmented distilled water are then added, and the haze is ready for use.

The barium chloride and magnesium sulphate solutions have had to be freshly made up at frequent intervals, for, for some reason, at the end of ten or fourteen days the haze produced by mixing them together has generally perceptibly diminished in depth. Dr. Wynn has recently suggested that, with such dilute solutions, the alkali of the ordinary glass bottle may in some way affect the reactions. The chemistry of the suggestion does not seem very clear, but since I have kept the solutions in bottles thoroughly treated with hydrochloric acid, the alteration in the haze has been distinctly delayed, and I am not sure that it may not be abolished altogether. I prefer, however, to make up the solutions afresh at least once a month.

I do not attempt to graduate the tube used for making the dilutions, for it is impossible to adopt any satisfactory scale of graduation in dealing with a substance that varies so greatly in amount, and the presence of graduation marks seriously interferes with the matching of the hazes. I therefore carry out the dilutions by means of a graduated cubic centimetre pipette, counting their number as I go along. The quantity of urine taken for dilution varies according to the amount of albumin contained—it may be convenient to take anything from a cubic centimetre to a tenth of a cubic centimetre. Should the urine be so heavily albuminous that the precipitate comes down in flocculent form, preliminary dilutions with water must be carried out to the necessary extent, and the results of the measurement multiplied by the number of preliminary dilutions.

Given a good light and a dark background against which the hazes are matched, the procedure is by no means a difficult one. But correctness of measurement depends upon keeping the fluids in the two tubes at the same level

² A larger quantity of Bismarck brown will be needed if the solution used is not freshly prepared.

of pigmentation, for any attempt to match together hazes contained in fluids of different degrees of pigmentation results in great inaccuracy. For this reason, the process of dilution is carried out with water pigmented as in solution 3. But, more often than not, some adaptation of the pigmentation has to be carried out as the process of dilution proceeds. Thus, if a highly coloured urine is being estimated, the first few dilutions must be made with plain, instead of pigmented, water, until the colour of the standard fluid is arrived at. If, on the other hand, the urine examined is of a lighter colour than that of the standard, a trace of Bismarck brown must be added. Afterwards, the process is completed by means of the ordinary pigmented water.

One of the chief obstacles to accuracy lies in the difficulty of obtaining complete precipitation of the albumin. For very small quantities, heat, with the addition of acetic acid, can be relied upon. But, with any appreciable degree of albuminuria, complete precipitation cannot be easily ensured by this method.³ Salicyl-sulphonic acid is a safe precipitant; but, in order to retain the precipitate in large dilution, this reagent must be in material excess, and this involves an undesirable amount of dilution, whilst its colour adds to the difficulty of obtaining a good match. The colour of picric acid, again, makes it unsuitable for the purpose. After trying a large number of expedients, I have come to the conclusion that the substitution of a few drops of salicyl-sulphonic acid for acetic acid, after boiling, almost invariably gives a complete precipitation of the albumin, and this can be quickly tested. In any case, the same method must be used throughout the investigation of any single case, for the hazes produced by different methods of coagulation are not always of the same degree of density, as measured against the standard.

I take the haze, produced as described above, as my unit of albumin. Although I have repeatedly measured it against an artificially albuminous urine made by dissolving a known quantity of dried albumin in an albumin-free urine, and I know its approximate value as estimated by myself (its percentage is low down in the third place of decimals), I think that it would be most undesirable to claim for the unit an absolute value. The object of my investigation is to obtain a picture of the comparative output of albumin at different periods of the same case. To maintain that the unit has an absolute percentage value, running into several places of decimals, would be to claim for the method a degree of accuracy which I do not think it can satisfy. My charts are therefore all expressed in terms of 'units of albumin'.

In order to find out the degree of accuracy attained in matching my hazes, I subjected myself to a series of tests. In each case, an albuminous urine was taken, and a series of dilutions, in as complicated a form as possible, were made with an albumin-free urine of an equal degree of pigmentation. The quantities of each urine used were noted on a piece of paper. Equal quantities of each dilution were then placed in the requisite number of test-tubes, so that each tube contained the same quantity of a similarly pigmented urine, and no hint of the

³ This has been shown by Dr. E. Wordley, this Journal October 1920.

strength of the contents could be obtained from their appearance. The tubes were stoppered with numbered corks, and the numbers covered over with slips of paper, and they were then thoroughly shuffled, generally by my house physician, and placed in the rack in any order that came to hand. The corks were removed and placed, number downwards, in order on the table, and I then made and recorded my estimations, after which the tubes were identified by means of the corks, and the relative strengths of their contents calculated from the written data, taking my highest estimation as the standard of comparison, that being the point most strongly against me.

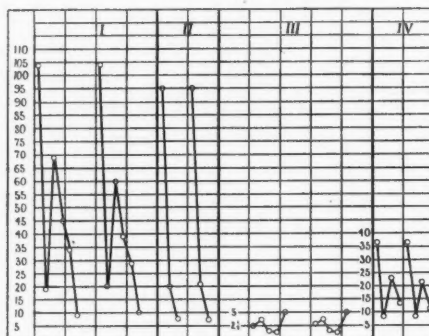


CHART I.

Chart I shows the result of four consecutive tests, carried out at considerable intervals. Each pair of curves represents a single test, the first of the pair representing my own estimations, the second the result that I ought to have arrived at.

The first test was carried out early in my experience, and leaves much to be desired, for only three of the six estimations are essentially correct. The second took place some weeks later, when I had gained experience, and had more fully worked out the conditions needed for success. Six dilutions were made, but I was unfortunately called away after the first three had been estimated. These three estimations are entirely correct, except for an error of one unit in the second entry. In the third test, a slightly albuminous urine was chosen, in which the quantity of albumin was quite unmeasurable by the Esbach method—indeed, the amount is so small that, in order adequately to represent the dilutions, I have had to double the scope of the scale. The results were all practically accurate within the terms of measurement of the chart. The fourth test was carried out a few months ago. There are some small inaccuracies, but the picture of the albuminuria is essentially true.

I do not claim that all my estimations reach this degree of accuracy. Dark days, hurried work, and personal conditions all have their effect. But that the method is capable of giving a reasonably reliable picture of the variations in the output of albumin occurring in any given case, I have but little doubt.

Description of Results.

Case I. Having provided myself with a method for the graphic record of albuminuria, I proceeded to apply it to the study of a case of orthostatic albuminuria in one of my wards in the Birmingham General Hospital, and eventually to the study of the nature and bearing of the orthostatic reaction in albuminuria in general. The patient was a girl, 8 years of age, in apparently perfect health. The heart was not enlarged, and the systolic blood-pressure was persistently below 100. Tests of renal function were entirely satisfactory, and no casts of any sort were at that time discoverable in the urine. But there was one point of great suspicion, namely, that the albuminuria was first noticed either during or immediately after an attack of diphtheria.

The urine secreted in bed was generally, but not always, quite free from albumin, and the comparatively few observations made in the late afternoon and evening showed as a rule a tendency to the well-known 'cyclical variation'.

Thus, Chart II, representing the hourly excretion of albumin during a certain twelve-hour day, gives a quite characteristic picture of what is expected from an orthodox case of orthostatic albuminuria, except that, on the day in question, the early morning (bed) urine contained a trace of albumin.

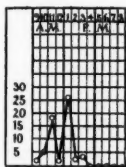


CHART II (Case I).

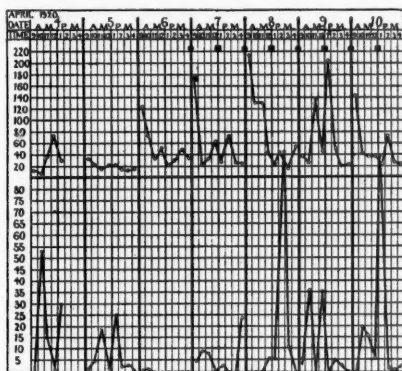


CHART III (Case I).

The next three charts contain records of the urine and albumin excretion throughout consecutive hourly periods of nineteen nearly consecutive days. (A chart of the preceding fortnight, with less complete observations, is omitted in order to save space.) In each chart the upper series of curves represents the volume of urine passed at each hour, measured in cubic centimetres. The lower curves represent the albumin content of each specimen, recorded in terms of 'units'. At the top of each chart are records of the amount of fluid taken during the period of observation: a black circle represents the taking of 5 oz. of fluid, an oblong that of 10 oz.

In Chart III, consecutive hourly measurements were made from 9 a.m., when the child got out of bed, to 4 p.m., and the following points are to be noted:

1. The bed urine is here only entirely free from albumin on three of the days. The four o'clock urine is free, except on two days, on one of which a large albuminuria was recorded. I thought that the morning journey to the lavatory might possibly account for the trace of albumin often present in the first specimen, but washing in bed and the use of the bed-pan did not abolish it.

2. On April 6 there was almost complete absence of albumin throughout the morning and afternoon, and another similar occurrence was noted in the chart omitted. Yet on that day, to my knowledge, the child was as active as on any other, and, being much interested in the other patients and in the life of the ward, she spent much of her time on her legs.

3. The two remarkable peaks of albuminuria occurring early in the afternoons of April 8 and 10 were again without adequate explanation: the Sister of the ward was unaware of any particular length of time spent in the standing position.

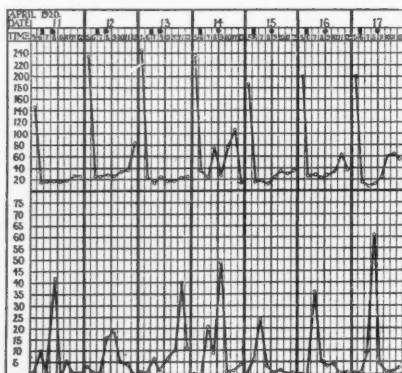


CHART IV (Case I).

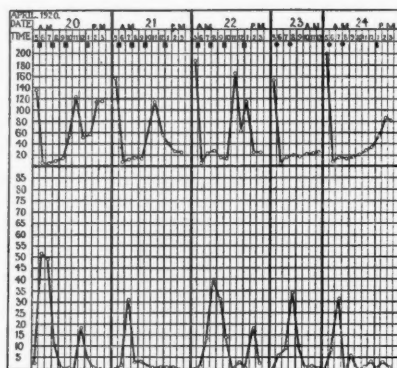


CHART V (Case I).

4. In this, as in all my charts, a high degree of albuminuria is invariably associated with a scanty output of urine, whilst the converse is not true, many equally scanty specimens containing little or no albumin. So long as the urine output remains uniformly scanty, as on April 5 in this chart, and on April 11, 12, and 13 in Chart IV, this gives rise to an appearance of complete absence of relationship between the two factors, urine and albumin excretion, and I believe that the explanation lies in variations in the length of time spent in the standing position. But as soon as the output of urine begins to vary (apart from the exceptional day, April 6), a tendency towards a definite inverse relationship of direction is evident between the two curves. This is well seen in the entries of April 4, 7, and 9 in Chart III. On the other hand, the continuous large diuresis of the three first hours of April 8 put an end to the output of albumin.

Chart IV represents the urine and albumin excretion over eight consecutive hourly periods from 5 a.m. to noon, and Chart V, with one exception, the excretion during ten hourly periods from 5 a.m. to 3 p.m. Most of the features presented in Chart III are again seen, except that the bed urine is much more frequently

free from albumin. In Chart IV, 15 oz. of fluid were given during the morning, and a very scanty secretion of urine resulted. In Chart V, for the first three days, 10 oz. of milk were given at 6 a.m., 10 oz. of milk and water at 8, and 10 oz. of water at 10, and I would call attention to the rather striking curve of urine secretion, a curve showing marked delay in diuretic response, followed by a sudden and temporary spurt of diuresis. This curve makes its appearance under similar conditions in not a few of my charts. I may state here that I have given the same quantities of fluid to a large number of apyrexial patients in my wards, suffering from all varieties of illness, and that the curve has only been met with in cases of apparently orthostatic albuminuria and nephritis.

Having now established a sort of picture of the albumin and urine excretion, I proceeded to investigate the conditions influencing that excretion. Frequent variations were made in the diet, without in any way affecting the albuminuria.

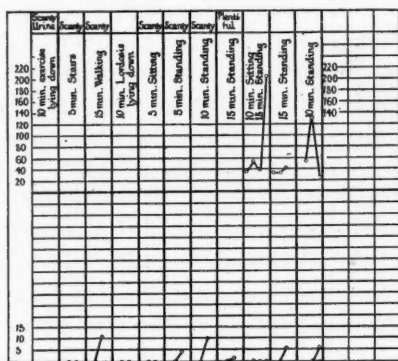


CHART VI (Case I).

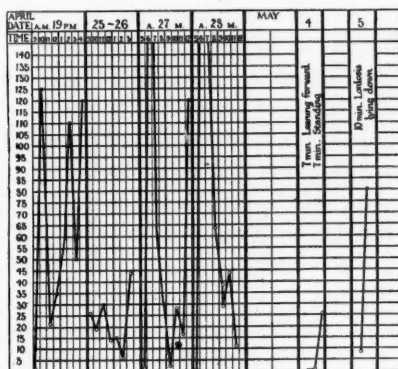


CHART VII (Case I).

The effect of exercise was tested both in the horizontal and upright positions. For the former, weights were attached to the legs by means of cords running over pulleys at the end of the bed, and for periods of five or ten minutes the child vigorously pulled the weights up and down. The urine, before and after the experiment, was free from albumin. On two occasions she got out of bed, passed urine free from albumin, and then ran up and down stairs for five minutes, getting back to bed and passing urine afterwards as quickly as possible. The specimen was again free from albumin. But fifteen minutes' walking produced eleven units of albumin.

Ten minutes of artificial lordosis in the horizontal position caused no albuminuria, and five or ten minutes' sitting was always without effect. But standing for various periods invariably set up an albuminuria, except on one occasion (last entry but two on Chart VI), when a period of fifteen minutes' standing happened to coincide with the occurrence of a profuse diuresis, and here no albumin was produced. The preceding entry also records a very small response to fifteen minutes' standing, and here again the urine was plentiful.

At this point the child went home, and I did not see her again for a year, when she came again into hospital. The general condition was as before. But the urine at first showed a definite bacilluria, which quickly cleared up with urotropine, and on one occasion we succeeded in finding a hyaline cast.

An extreme change had come over the albuminuria. It was still mainly orthostatic, though the bed urine was now only exceptionally quite free from albumin. The slight albuminuria of the horizontal position seemed, however, to be still postural in origin, for it could be abolished by taking away the pillows and making the child lie absolutely flat in bed. But the albuminuria of the upright position was now enormous, and was often so great as to be beyond the limits of representation in the chart (Chart VII). Further, on April 19 the 4 p.m. urine contained 120 units of albumin. Ten minutes of artificial lordosis in the horizontal position now raised the albumin content of the urine from 8 to 80 units, whereas in the previous year no albuminuria had been produced.

Some further observations were made with regard to the effect of position. On May 4 the bed urine contained no albumin. The child then stood for seven minutes, leaning well forward against a low support. The urine passed directly afterwards contained only one unit of albumin. She then stood upright for the same length of time, with the result that the albumin rose to 26 units. This shows—a well-known fact—that it is the vertical (?lordotic) position of the trunk that is immediately responsible for the albumin leakage. It further shows that the sensitiveness to the standing test had greatly increased during the year.

The later day tendency to cessation of the albuminuria in orthostatic cases still remained for investigation. It has sometimes been suggested that this is due to adaptation to the upright position gradually acquired in the course of the day, but it is more often acknowledged as a frankly cyclical variation. In order to investigate this question, two experiments were made. On April 26 the child remained in bed throughout the day, and got up for a few hours during the night, passing urine at hourly intervals. The records on the chart show the contrast between the albuminuria so produced and that recorded in the upright position during the day. On three other days she remained altogether in bed, except that she stood up for stated periods at different times of the day. The results are recorded in Chart VIII. On the first day, standing for seven minutes was carried out at 11 a.m., 2 and 6 p.m. The response steadily diminished, and at 6 o'clock a very small albuminuria resulted. On the second day the child stood for five minutes at a time on five occasions. There is again a gradual drop in the amount of albumin produced, but the result is less definite than before. And on the third day, with periods of standing of the same duration as on the preceding day, quite small and irregular quantities were produced. The variability of response under apparently similar conditions is, I think, one of the remarkable things about this and allied cases, but this experiment seems to suggest that the tendency to diminution in the later day output of orthostatic albumin is not dependent upon any acquired adaptation to the upright position, but is a true cyclical variation.

In the rest of my cases I have aimed only at investigating the chief points suggested by the foregoing study.

Case II. The second patient, sent in as a case of orthostatic albuminuria, was again a girl, aged 11. She was described by her mother as being out of health, easily tired, and generally 'run down'. She was a pale and rather lethargic child, not inclined to take much exercise, and, unlike her predecessor, prone to sit about, and showing but little interest in the life of the ward. The heart was not enlarged, the systolic pressure generally about 100, and at that period no casts were found in the urine. Tests of renal function were satisfactory.

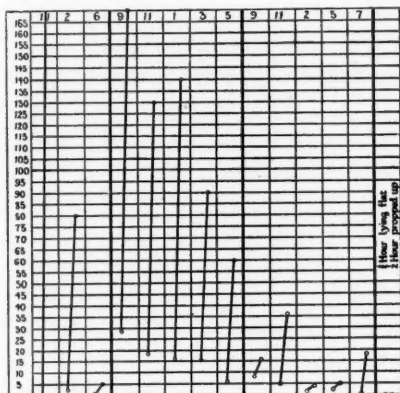


CHART VIII (Case I).

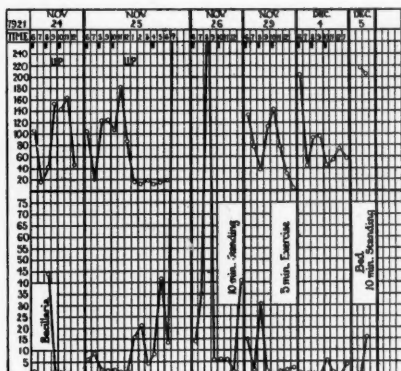


CHART IX (Case II).

The urine at first showed a definite morning albuminuria, and on several occasions this reached a considerable degree. But there was at that time a severe bacilluria, which quickly cleared up under treatment, and then the bed urine was either albumin-free or contained a very small amount. But again there was not the invariable complete absence of albumin in the urine of the horizontal position that is supposed to characterize these cases. So far from showing a cessation of the albuminuria in the later hours of the day, there was a steady increase on Nov. 25, and the 7 o'clock urine contained 205 units of albumin.

There was a very pronounced orthostatic reaction, and the amount of albumin shows enormous variations. Standing for ten minutes on Nov. 26 raised the albumin from a scarcely recognizable trace to 41 units. Five minutes' running up and down stairs on Nov. 29 only produced an extra half-unit. But it is noticeable that the curve of urinary secretion, after taking 10 oz. of fluid at 6, 8, and 10 a.m., does not show the tendency to delay in diuretic response observed in the former case. The child was put on good doses of calcium lactate from Dec. 2 to Dec. 8, and some diminution in the quantity of albumin appeared to result. The inverse relationship of urine and albumin excretion, noted in the former case, is often in evidence.

On Dec. 10 the effect of standing at different periods of the day was investigated, the child remaining in bed throughout the day except for three periods of standing of ten minutes each, at 12, 2, and 6 o'clock, and here there was complete absence of albumin production at the 6 o'clock experiment. This seems to demonstrate that the later day cessation of the albuminuria, when it occurs, is a truly cyclical variation, but the explanation is yet to be found. But that there is no invariable rule in the matter is shown by a repetition of the experiment on Dec. 17, when the albumin produced by standing at 5.30 p.m. is only less than that occurring at earlier periods. It is to be noted that on Dec. 17 seven minutes' standing in the leaning forward position produced no albuminuria. Seven minutes spent in the upright position then produced 4 units, and twenty minutes after getting back to bed the amount had risen to 23 units, showing that the effect of standing is not immediately abolished by the resumption of the horizontal position.

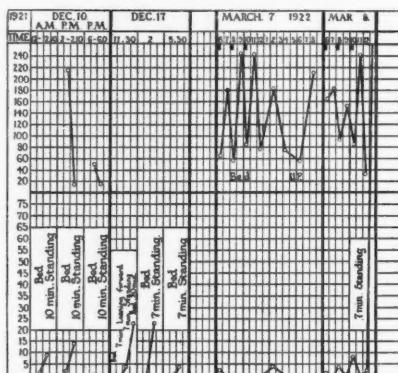


CHART X (Case II).

The last two records on the chart refer to a period of readmission, three months later. The amount of albumin on March 7 and 8 is quite small, but at 7 o'clock on March 8 seven minutes' standing upright produced an albuminuria altogether beyond the capacity of the chart to register. If one compares this result with the small effect produced by ten minutes in the upright position on Dec. 17, it must be admitted that the habits of albumin production in these cases contain much that needs explanation.

These two cases are the strongest claimants to a place in the group of functional orthostatic albuminuria that in the course of two and a half years' search I have been able to obtain for investigation. Yet on systematic study they fail in several particulars to conform to the conditions generally accepted as characterizing that group of cases. My colleagues in the out-patient department of the General and Children's Hospitals have done their best to supply me with material for my study, but all the cases sent into my wards with the provisional diagnosis of orthostatic albuminuria have broken down more or less on systematic investigation.

Case III. The next case may be very briefly described. It seems to form a sort of connecting link between the first two cases and those of nephritis to be subsequently recorded. The case was that of a lad, 18 years of age, who was brought to me by his doctor with the diagnosis of orthostatic albuminuria. The chief complaint was that he was below the height and weight usual for his age, and a routine examination had shown the presence of albumin in the day urine. The urine secreted in bed had been found to be free from albumin, but the specimen brought for my examination contained a small amount. That passed in my rooms contained a large quantity, and the amount was markedly increased by ten minutes' standing. The systolic blood-pressure was 125, a shade high for the age.

Urine was passed every hour one day from the time of getting out of bed (8 a.m.) to 8 o'clock at night, and the specimens were sent to me for examination.

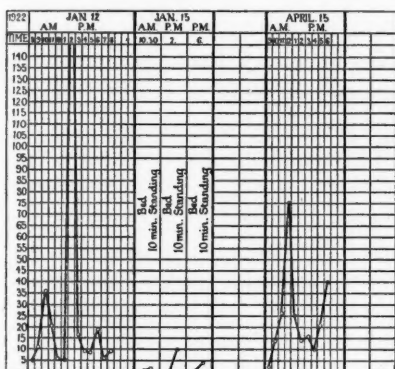


CHART XI (Case III).

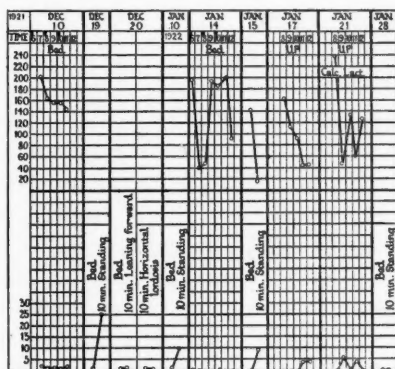


CHART XII (Case IV).

The morning urine was by no means free from albumin, and the albuminuria does not cease in the later hours of the day. But there was one of the remarkable peaks of albuminuria that seemed to me at that time characteristic of the functional group. I should add that no casts were found.

On another day the boy remained in bed, and stood up for ten minutes at a time on three occasions. The results show no evidence of a cyclical tendency. Another set of hourly specimens sent to me three months later tell much the same story as before.

With the idea of aiding his development, the boy had been given large quantities of meat by his parents. On a restricted diet, and with some rules of healthy living, he has slowly improved, and on a recent examination I found the systolic pressure 114, and the quantity of albumin much reduced, though it was still considerably increased by standing.

I began this study with the usually held opinion that these cases of orthostatic albuminuria form a group by themselves, conforming to certain definite conditions, and owning a pathology outside the kidney. But when I found all the cases sent to me with that diagnosis—and those I have recorded are only

a selection—failing in one particular or another to satisfy the accepted criteria, and when case after case raised some point of suspicion with regard to the kidney, it was inevitable that I should begin to question their 'functional' nature. I therefore felt that the next step was to see for myself in what way cases of nephritis and cardiac albuminuria differ in their reactions from those of the accepted orthostatic group.

Cases of acute nephritis, with their large albuminuria and haematuria, were unsuited to my purpose. But I was fortunate in having sent into my wards several cases of much milder type—cases either with no symptoms or giving a brief history of malaise and oedema, and showing albumin and casts in the urine, and occasionally a few red cells in the centrifugalized deposit. Four cases may be recorded in illustration.

Case IV was that of a boy, 12 years of age, who was admitted with oedema of the face and a definite subacute attack of nephritis. On admission there was a considerable amount of albumin in the urine, but after a few days in bed the oedema cleared up and the albumin subsided to a very small quantity. On Dec. 10 successive hourly specimens showed a maximum of 2 units, and on Dec. 19 the bed urine contained only $1\frac{1}{2}$ units. The boy then stood for ten minutes, and, after getting back to bed and passing urine again, 25 units were measured. Next day, ten minutes' standing in the leaning forward position, and ten minutes of artificial lordosis lying down, produced no increase in the albuminuria, but on Jan. 10 and 15, when on both occasions the bed urine was practically free from albumin, ten minutes' standing produced an albuminuria of 10 and 9 units. On Jan. 14 the bed urine was almost free from albumin, but on getting up on Jan. 21 a small albuminuria was recorded.

The reactions here were those of the official orthostatic group. But it is to be noted that on Jan. 28 standing for ten minutes produced no albumin. The eventual cessation of the immediate orthostatic reaction, as decided by the standing test, with an albuminuria of the continuous upright position, will be found in the remaining cases of nephritis, and for convenience of reference it may be called the 'delayed orthostatic reaction'.

Case V was instructive. The patient was a boy, 14 years of age, who came into hospital with a clear subacute attack of nephritis, oedema of the face and limbs, albumin, and casts. The albumin steadily diminished with rest in bed, and on Feb. 9 the quantity was quite small. At the end of the morning the boy stood for ten minutes and produced only an extra half-unit of albumin, but at the time a large quantity of urine was being excreted.

Although he was kept in bed on a flesh-free diet, for the next few days the amount of albumin in the twenty-four hours' specimen showed a definite increase. Hourly specimens were therefore again examined on Feb. 16, with a striking result. The night urine contained 4 units of albumin, 7 a.m. specimen was almost free, but at 8 o'clock the amount suddenly rose to 87 units, to fall again to 4 at 9 o'clock. At the end of the morning, ten minutes' standing produced an increase of 38 units, in marked contrast with the former experiment.

Inquiry showed that between 7 and 8 a.m. the boy had had a warm lysol bath (he was the victim of a severe scabies), and it was evident that the bath had not only produced a large temporary albuminuria, but had also caused a greatly increased susceptibility to the upright position. The bath was at once countermanded, but next day the 8 o'clock specimen contained 240 units of albumin. All that had happened between 7 and 8 o'clock was that the boy had sat up for a short time whilst his bed was being made. Next day, bed was uninterrupted, and the amount of albumin was almost negligible.

Tests of the effect of the standing position were now carried out at weekly intervals as a guide to treatment. On Feb. 25 seven minutes' standing raised the albumin from 4 to 90 units, and half an hour after getting back to bed the amount had risen to 120 units—an event similar to that noted in Case II. Earlier in the same morning, seven minutes spent in the leaning forward position had only produced an extra half-unit. A week later, seven minutes' standing produced at once 120 units, and I feared that permanent mischief had

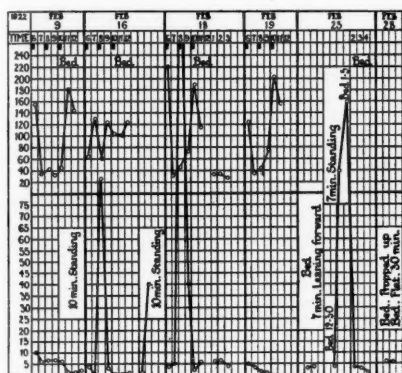


CHART XIII (Case V).

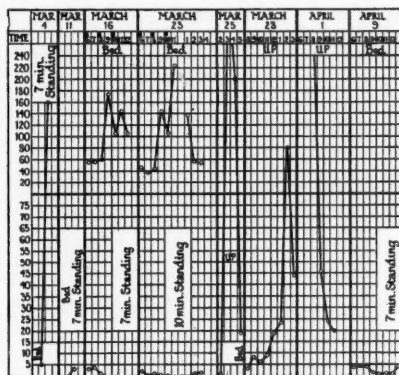


CHART XIV (Case V).

been done. But the following week the same period of standing only produced 3 units, and a few days later still, none at all. On March 16 and 23 the bed urine was to a large extent free from albumin, and on the 25th I allowed the boy to get up for two hours in the afternoon. A huge albuminuria at once developed, and the rapid fall on getting back to bed is recorded on the chart (Chart XIV). The remaining entries speak for themselves.

This case, at one period, again gives every one of the official orthostatic reactions, except that there is no tendency to a later day cessation of the albuminuria. The 'delayed orthostatic reaction' of the preceding case is again noted—ultimately, ten minutes' standing produced no albumin, but a very large albuminuria had developed at the end of the first hour after getting up.

Case VI may be quickly disposed of. It is included because it gives, in a case of probable mild nephritis, marked examples of the characteristic curve of delayed response to the intake of the routine 30 oz. of fluid, and also shows the tendency to the inverse relationship of the curves of urine and albumin excretion

already noted in several of my cases. The patient, a boy aged 15, had recently been referred for insurance in the Post Office on account of the presence of albumin in the urine, and he was sent into my ward as a probable case of orthostatic albuminuria. No casts were found in the urine, but on admission the systolic pressure was 134, and with continued rest in bed it did not fall below 125. Urea concentration was not satisfactory. The bed urine was rarely free from albumin, standing at different periods of the day gave rise to very irregular degrees of albuminuria, and getting up resulted in a large albuminuria.

Case VII is a striking example of orthostatic albuminuria, apparently of nephritic origin, but it differs from Cases V and VI in that there were no symptoms. It also illustrates the difficulty which these cases may cause in the matter of acceptance for life insurance.

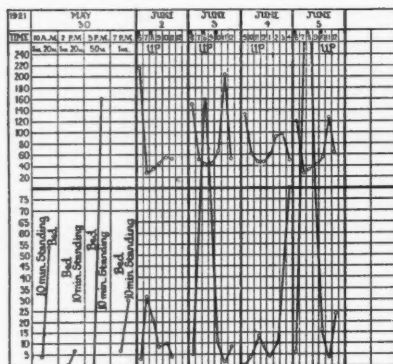


CHART XV (Case VI).

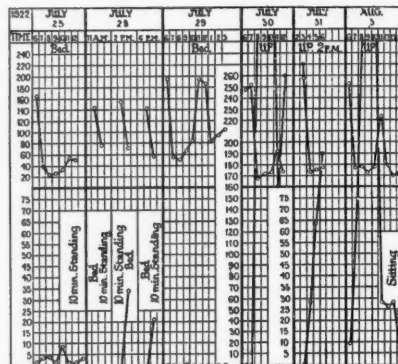


CHART XVI (Case VII).

The patient was a lad, aged 17, who, seven weeks before I saw him, had been accepted for insurance as a bank clerk. Albumin had been found by the examining doctor, but the boy was assured that it was of no importance, and he was passed as a first-class life. His mother, however, sent him to the family doctor, who found casts in the urine. The boy was kept in bed for a week, when both albumin and casts disappeared. On getting up, both returned, and he was kept in bed again for a period of three weeks, with the result of cessation as before. Again, on getting up, the albuminuria and casts returned, and at this stage he was sent to me for an opinion. The urine passed in my rooms was loaded with albumin, and the centrifugalized deposit contained one of the largest collections of casts I have ever seen. The systolic pressure was 120.

I took him into hospital for investigation. On the second day spent in bed, several hourly specimens were examined, and each one was free from albumin, but on this day there was throughout a considerable diuresis. The following day (first entry on the chart) the curve of urine secretion showed the characteristic delay on the administration of the routine 30 oz. of fluid, and a small bed albuminuria was registered. At the end of the morning the boy

stood for ten minutes and produced only an extra unit of albumin. On July 28 he remained in bed all day, except that he stood for ten minutes at 11 a.m., 2 and 6 p.m. The bed urine on each occasion was free from albumin. The morning standing produced nothing; at 2 o'clock 34 units, and at 6 o'clock 21 units were measured—a sort of inverted cyclical variation. Fish had been taken for dinner at 1 p.m., but that this was not the cause of the albuminuria is shown by the next day's observations—the bed urine was entirely free from albumin from 6 a.m. to 3 p.m., except for a trace in the 9 o'clock specimen. On July 30 he got up at 6 a.m. and passed hourly specimens till noon. The 6 and 7 o'clock specimens were albumin-free, but both were plentiful in quantity. The albuminuria of the remaining specimens, when the urine was scanty, was so enormous that, in order to get any of them on the chart, I have had to halve its scope. Even then, three of the measurements are altogether out of the chart. On the previous day, when there was no albuminuria, casts had been absent from the centrifugized deposit, but the second of the highly albuminous specimens of July 30 contained a moderate number. The curve of delayed response to the intake of fluid was again observed. Next day he got up at 2 p.m. No albumin was present in the 3 o'clock specimen, and then there was a steady rise in the quantity, with an almost uniform urine output.

Although I was quite unable to feel either kidney, and the abdominal muscles were strong, I tried the effect of wearing an abdominal belt, with pads over the kidneys, on two of the mornings. But, although the quantity of albumin was a little diminished the first day, it was as big as ever on the second. On Aug. 3 the boy was up from 6 a.m. A very large albuminuria was recorded up to 10, but the 11 and 12 o'clock specimens were only moderately albuminous. He then sat for an hour. At the end of half an hour 28 units were measured: twenty minutes later there were only 4. In all probability these two amounts were the residue of the previous orthostatic albuminuria, and I take the observation to imply that sitting abolishes the albuminuria—another point of similarity with the more typically orthostatic cases.

The urea concentration was tested on three occasions, and gave results that appeared to point to a difference in concentration in the horizontal and upright positions. The first test (in bed) may be discounted, as it coincided with a large and persistent diuresis, and I have therefore omitted it. The second and third tests gave the following results:

I. In bed:

		c.c. urine.	Urea %.
5 a.m.	Urea given	191	1.3
6 "		51	1.3
7 "		220	2
8 "		45	1.9

II. Up:

5 a.m.	Urea given	245	1.05
6 "		51	2.5
7 "		50	2.7
8 "		40	3.4

The conditions of the two tests were exactly the same, with the exception of position. The results are contradictory: the bed concentration seems to suggest slight impairment of renal function, the upright test gives good results. Perhaps the fact of exercise may explain the discrepancy, but a patient with normal kidneys gave approximately the same concentration in bed and when up. I have no doubt that the bearing of the upright position on urea concentration has been investigated, but I do not know of observations of the point. It seems one worth looking into in cases of nephritis.

I had originally intended to follow up my study of the effect of the upright position in cases of mild nephritis with a similar study of the albuminuria of cardiac failure. But I have found this a very difficult matter. If there is a material albuminuria, the patients are generally too ill for investigation, and the urine is too scanty for hourly passage; whilst cases fit for study usually have little or no albuminuria. Of the orthostatic reaction in cardiac failure, therefore, I have but little knowledge. In the records of the continuous output of urine and albumin in the few cardiac cases that I have yet been able to study, some have shown an almost constant proportional albumin content—the entries on the chart have formed an almost straight line. Others have given the inverse relation between the two factors. The cases, however, are too few in number to be worth quoting in detail.

Discussion of Results.

Before attempting to discuss the points emerging from the study of these seven cases (and others like them), an obvious criticism must be dealt with, namely, that my first cases are not true instances of orthostatic albuminuria, and that I have not brought forward a single example of the condition—a criticism with which I should not be disposed to quarrel. Indeed, when, a year ago, I showed the charts of my first case at the Birmingham meeting of the Association of Physicians, that criticism was actually made, and it was pointed out that none of the accepted criteria for the diagnosis was uniformly satisfied. And the same remark holds good still more for the other cases.

Now, if those conditions be really invariably true at all times of the orthostatic cases, then, in the course of two and a half years' search, neither I nor my colleagues in the out-patient room have come across a single instance of the disorder. Yet it is generally held to be of common occurrence. With the greatest kindness, Dr. Simey, the medical officer of the Rugby School, took the trouble to collect for me one evening eight of his most marked cases of 'functional' albuminuria. It is true that Dr. Simey did not claim that these were orthostatic cases, but in such a collection one would expect that so common a form would at least be represented. Yet, although there was abundant evidence of excess of albumin in the next morning's urines over that observed at night, not one of the boys passed albumin-free urine that evening, when I was most kindly invited to examine them.

On the other hand, I would point out that these orthodox conditions were very fully satisfied in Case I on many of the days, and that on those days the case would seem to belong to the orthostatic group, and, I am sure, would have been so classified by any one seeing it. And I think I may claim that the case was subjected to an exceptionally prolonged and continuous examination. Moreover, my standard of albumin estimation is a severe one, and the 'unit' is easily missed if not carefully looked for. At all events, the result of my study has been to leave me with the impression that these supposed essential conditions are nothing more than the expression of certain tendencies which, on different occasions, may or may not be completely observed. My own objections to the diagnosis are more fundamental, but, for clearness of reference, I shall continue to speak of the members of the first group as cases of 'orthostatic albuminuria'.

A second criticism might be made in the opposite direction, and it might be maintained that I have diagnosed as nephritic cases rightly belonging to the orthostatic group. As the grounds for the differentiation are stated in each case, I may leave readers of this paper to classify the cases as seems to them best. A somewhat raised blood-pressure, casts (other than hyaline), oedema, and in two cases an impaired urea concentration, have been my own reasons for the distinction. But casts may arise from circulatory stasis.

Any discussion of the bearing of these cases on the question of the pathology of orthostatic albuminuria can only deal with the two factors investigated, urine and albumin excretion. Needless to say, there are many other points that should be considered—relation of globulin to albumin content, specific gravity, coagulability of the blood, &c. These were all investigated in Case I, with results that in general conformed to the usually accepted criteria, and some were observed in others of the cases. But lack of time has made it impossible to go very fully into these matters in all the cases. I do not greatly regret the restriction, for I think I shall not go far wrong in dealing with the question from the broad standpoint of excretion. I may, however, say that I have not been able to find any substantial difference in the two groups of cases in the matter of albumin-globulin ratio. Many of the urines passed by the nephritic patients have contained a large proportion of globulin, as shown by precipitation by acetic acid in the cold, and in one of these cases (oedema and casts) a larger proportional precipitate of globulin was obtained in some of the hourly specimens than in any of the more obviously orthostatic cases.

It is impossible to enter into a detailed review of the very extensive literature which has grown up around the subject of orthostatic albuminuria without unduly lengthening my paper. Moreover, were I to attempt to do so, I should only be copying the very thorough reviews published by Hooker (*Archives of Internal Medicine*, 1910, p. 491) and Bass (*American Journal of Diseases of Children*, 1912, p. 246). Briefly, the outcome of these reviews seems to be that there are three main views as to the pathology of the condition. According to one group of writers, the explanation is mechanical or anatomical.

Most commonly, the albuminuria is held to be due to lordosis or some other spinal deformity which brings about a condition of circulatory stasis in the kidney in the upright position. The second group of writers maintain that, whether or no lordosis or other anatomical peculiarity is immediately responsible for the appearance of the albuminuria, some undue renal permeability must be invoked before an adequate explanation can be arrived at. The third group places the responsibility primarily on the circulation, whether through cardiac weakness or abnormality, or through some vasomotor disturbance, and Professor Cushny, in his book on the Secretion of Urine, lends his support to this belief. In my own cases I have seen nothing to suggest that cardiac weakness has played any part in the causation of the albuminuria, and some difficulties that seem to me to stand in the way of a purely circulatory explanation will later be stated. It is with the second group of writers that I have been led to agree.

It is, however, to be noted that in some of the later papers included in Bass's review the orthostatic albuminuria of mild nephritis receives full recognition, and there is a tendency to arrange the cases in groups according to the nephritic or non-nephritic evidence of the urine and other matters. Further, the relation of oliguria to the appearance of albumin in the urine receives attention in more than one paper.

It must at once be admitted that spinal position with its circulatory consequences is the determining factor in the production of the albuminuria. Experiments on rabbits have shown that a continued severe lordosis is itself sufficient to produce, not only an albuminuria, but also an actual nephritis. Several cases of pseudo-hypertrophic muscular paralysis, with of course extreme lordosis, have been recorded in which there has been an orthostatic albuminuria, though I have seen for myself that the association is not invariable. Again, there is at least one case of lateral curvature on record in which ureteral catheterization has proved that an orthostatic albuminuria came from one only of the two kidneys. Further, my own cases have invariably shown that, at a time when standing upright produced a definite albuminuria, standing in the leaning forward position abolished the production, and this has been true of the orthostatic and nephritic cases alike. The fact is well known in orthostatic albuminuria. I do not know whether it has been observed in this type of nephritis.

But, while it is certain that spinal position immediately determines the onset of the albuminuria, I am not convinced that this is the whole matter, at any rate in the bulk of the cases. It is to be noticed that each of my first three cases—all of them sent to me as cases of orthostatic albuminuria—raised some point of suspicion with regard to the kidneys. In the first case of all, the albuminuria was first discovered either during or immediately after an attack of diphtheria—surely a most suspicious point. And this case was by far the nearest to the official type. The second patient came in with an intense bacilluria. And in the third the blood-pressure was somewhat too high for the

age. Case VI, again, sent into hospital as a case of the orthostatic group, showed a bed urine sometimes practically free from albumin, with an intense albuminuria of the upright position, but the blood-pressure was persistently raised; and the urea concentration was not satisfactory. For these reasons it is included amongst the cases of nephritis, though no casts were found in the urine.

In the first case, during the first period of examination, the albuminuria was comparatively moderate in amount, artificial lordosis in the horizontal position produced no albuminuria, and the bed urine was mainly free from albumin. When the child was readmitted, a year later, artificial horizontal lordosis caused a pronounced albuminuria, and it was only in the absolutely flat position that the urine became albumin-free. Moreover, the albumin of the upright position had now become enormous. The case had therefore developed greatly in the course of a year, and it is hard to believe that such development could have been due to any change in the anatomical condition. The development may, perhaps, be explained as the result of damage to the glomerular capsule due to the habitual passage of albumin. At any rate, I think that there is no doubt that it was essentially a renal development.

The very first case of apparent orthostatic albuminuria that I remember was that of a boy who was brought to me many years ago on account of a general loss of health. He complained of headache, was losing weight, and had been doing badly at school. I found nothing on examination until I came to the urine, which was loaded with albumin, though the morning urine was free. On the strength of this fact, together with the absence of other signs of nephritis, I accepted the case without question as belonging to the functional orthostatic group, and with general treatment, especially abolition of cold bathing and avoidance of severe exercise, he rapidly improved, lost his headache and regained his weight. I did not see him again for three years, but then his urine was quite free from albumin, and he has since successfully passed through a long period of active service in the war. Has he lost a lordosis, or remedied some other anatomical peculiarity? Or is it not more probable that the general ill health and albuminuria were alike the expression of some mild and recoverable kidney infection? In that case, he also must be removed from the orthostatic group. But then, one is tempted to ask, where are the true cases to be met with? Those who examine large numbers of applicants for bank and Post Office insurance tell me that they see many examples. Case VII was accepted for insurance in a bank as a case of functional orthostatic albuminuria, and Case VI was referred from the Post Office on that ground, and both broke down on systematic examination.

It may be worth noting that Nassau (*Zeitschrift für kl. Medicin*, lxxxiv, 1917) subjected a number of German soldiers to the experiment of standing in an extreme position of lordosis, many of them for as long as an hour and a half at a time, the urine in each case being free from albumin at the beginning of the experiment. The soldiers were divided into two groups: one, convalescents from

various illnesses; the other, soldiers on active service. The convalescents gave the largest number of positive (albuminuria) results, 28.17 per cent. as compared with 22.6 per cent. of the supposedly healthy soldiers. But, of forty healthy civilians subjected to the same experience, only one produced an albuminuria. I am myself unable to produce any albumin by standing for ten minutes in the most extreme position of lordosis that I can assume. A young man, in apparently perfect health, but with a trace of albumin in his urine to start with, got a large albuminuria by exactly the same proceeding.

It is clear, from the charts of the cases of the mild type of nephritis that I have been studying, that, during and immediately after a subacute attack, the reactions of the albuminuria to the upright position are identical with those of the orthostatic group. Artificial horizontal lordosis is without effect: the bed urine may be quite free from albumin, but standing almost invariably produces an albuminuria. Standing in the leaning forward position and sitting (one case) abolish the albumin excretion. The same delay in the response to the taking of a fixed quantity of fluid is often seen in both groups, and there is the same inverse relationship of direction between the curves of urine and albumin output, except when the patients are up and there is a uniformly scanty secretion of urine. This relationship is of course best seen when the patients are out of bed, for often in bed the albuminuria comes to an end.

But two points of distinction have to be noticed. Cases I and II, the best examples of the apparently functional group that I have come across, were the only two in which any tendency to cyclical variation was observed, the tendency only appearing in Case II when the patient was in bed and stood up at stated intervals. In the nephritic group, no tendency of the sort was noted in a single instance. And, secondly, the cases of mild nephritis have invariably in the end lost their reaction to the ten minutes' bed-standing test, although remaining up for any length of time has always given rise to a definite, and usually large, albuminuria, and standing when up has, I think, always increased its amount. It seems as though, in general in the nephritic cases, it takes a longer time to establish the effect of the upright position. On the other hand, the response of the more obvious cases of orthostatic albuminuria has always been immediate, except in the presence of diuresis. This, it must be admitted, is exactly opposite to what would be expected, for it is in the nephritic set of cases that the greatest degree of glomerular damage must be assumed, and this, one would think, ought to translate itself into the more immediate response to the difficulty brought about by the upright position. To this objection I have no answer. The point seems to me as marked a distinction in albumin reaction between the two groups as any that has yet been established.

Rightly or wrongly, and in spite of the objection just stated, the impression has grown up in my mind that many at least of the cases usually diagnosed as instances of orthostatic albuminuria are not really 'functional' in nature—by which I mean that they possess a renal pathology. It may be said that my

examples of the orthostatic group are too few in number to justify any such conclusion. But for two and a half years I and my colleagues have been looking out for these cases, and the number sent to me with that diagnosis has been by no means inconsiderable. Yet not one of them has come out wholly unscathed from the ordeal of a prolonged examination. Indeed, the main result of the search has been to provide me with quite a large number of cases of this mild 'orthostatic' type of nephritis, of which I knew but little before. I cannot of course prove a negative, and it would be absurd to maintain that there are no cases of orthostatic albuminuria with a causation lying outside the kidney. I can only say that none of the cases sent to me, either in hospital or private practice, has satisfied me as to its functional nature.

By the possession of a renal pathology, I do not necessarily suppose an established nephritis, such as would be recognized *post mortem* by the means at present at our disposal. I imagine that something far short of that may be possible. That small and recoverable assaults upon the kidney (possibly 'toxic') are far from uncommon I am quite sure: one cannot interest oneself in the study of albuminuria without coming to such a conclusion. Whether or no some such explanation applies to orthostatic albuminuria can only be a matter of speculation. The one recorded case that I know of which has come to post-mortem examination showed only a minute focus of damage.

The mechanism of the orthostatic reaction, as one sees it in working, is to me difficult to understand. My charts show abundant instances of the great rapidity with which the response to the upright position takes place, and the amazing bulk of albumin often thrown out in a very short time. As shown in two of my cases, the effect continues for a brief period after getting back to bed, and then in an hour all is over and the urine is back to its original condition. We know that in cardiac failure prolonged and gradually increasing circulatory stasis is necessary before an appreciable degree of albuminuria is produced, and that even then the albumin may be quite moderate in amount. If orthostatic albuminuria is a mere matter of circulatory stasis, one has to imagine a stasis of severe degree setting in almost at a moment's notice, and the effects clearing up completely in the course of an hour. But if the glomerular capsule were itself abnormally permeable, a comparatively slight degree of stasis might be efficient. Possibly some light might be thrown on the question by the systematic study of the albuminuria of severe exercise and its relation to oliguria.

One of the most difficult points to understand, on the purely circulatory theory, is involved, as it seems to me, in the delay in the response to the intake of fluid, a delay often seen in the orthostatic and nephritic cases alike. The curve of delay is particularly well seen in the first three days recorded in Chart V. The response was extremely and steadily delayed—seldom more than 17 c.c. of urine were secreted during the first four hours of the experiment. Yet there is great variation in the amount of the albumin: many of the specimens contain but a very small quantity, others are grossly albuminous. But if the scantiness of urine is to be accounted for only by circulatory delay, the conditions for the

production of albumin are abundantly present throughout. Yet it is only when the upright position is assumed that the albumin becomes appreciable. Scantiness of urine appears to be essential for the production of the standing albuminuria in the orthostatic cases—fifteen minutes' standing produced none in my first case during a spurt of diuresis. But continued scantiness of urine is of itself insufficient to cause albuminuria without the aid of the upright position. In the nephritic cases it would seem reasonable to attribute the delayed secretion, partly at any rate, to the condition of the kidney. Can any such inference be drawn in the orthostatic cases?

Conclusions.

1. There appears to be a group of mild kidney lesions which, apart from subacute exacerbations, reveal themselves chiefly by the inability of the kidney to bear, without leakage of albumin, the circulatory disturbance brought about by the upright position. In spite of difficulties, which I have endeavoured fairly to state, I believe that the orthostatic albuminurias belong to the same group, though at its mildest extremity.

2. In none of the cases examined has the bed urine been always completely free from albumin.

3. The later day cessation of the albuminuria, in the few cases in which it has been observed, has also been variable in its occurrence. The cessation is not due to adaptation to the upright position acquired in the course of the day, but its explanation has yet to be found.

4. There is a close association between the quantity of urine secreted and the amount of albumin contained. In general, the two curves are inverse in direction, but the albumin excursions are probably exaggerated by the assumption of the upright position. Profuse diuresis generally puts an end to the excretion of albumin, even in the standing position. When the urine is persistently and abnormally scanty, the two curves cease to show any relation to one another.

5. Most of the cases examined have shown a marked delay in the secretory response to the intake of a fixed quantity of fluid.

6. In the more obviously nephritic cases, the albumin response to the upright position is not immediate, except during a subacute exacerbation. In the more definitely 'orthostatic' cases, standing at once and invariably gives rise to albuminuria, except during a period of diuresis.

THE FRACTIONAL TEST MEAL IN THE STUDY OF DISORDERS OF THE GASTRO-INTESTINAL TRACT (AN ANALYSIS OF 174 VERIFIED CASES)¹

By DONALD HUNTER

(From the Medical Unit, the London Hospital)

Introduction.

THE work of Rehfuß (1) in 1914 made practicable a method of investigation of gastric function by means of the fractional test meal. Since the publication of the original communications by Rehfuß and his co-workers, many papers have appeared recording the findings in normal and abnormal cases, and experimental results on the physiological activity of the stomach. It is not proposed in this paper to review the results of these communications, but merely to present the writer's own personal experience in the investigation of a series of patients, and particularly to attempt to place on a sound basis the clinical interpretation of the findings of the fractional test meal in disease of the upper abdomen.

The work recorded here commenced in July 1920 and has continued over a period of two years. Until October 1921 it was carried out as an individual research by the writer. Since that time it has formed part of the investigations carried out by the Yarrow Research into the causation of gastric ulcer. The work has dealt with a wide variety of clinical material, including in-patients and out-patients in the departments of medicine, surgery, and dermatology.

Charts have been drawn up of 270 test meals, but of these a verified diagnosis was possible only in 174 cases. In 165 of these the diagnosis was proved by operation, by biopsy, or by autopsy. Of the remaining 9 cases, in 6 a so-called primary anaemia was diagnosed by blood examination, and in 3 a skin disease was diagnosed clinically. I wish to emphasize, however, that the basis of the paper rests on 165 cases, where the condition of the abdominal organs was determined by actual inspection, supplemented where possible by histological examination of excised specimens. In the remaining 96 abdominal cases the diagnosis remains merely a clinical concept, and these have therefore been deleted from the series as manifestly useless.

The paper is arranged in the following sections: (1) An account of the

¹ This communication, with the addition of 270 case-reports and charts, was accepted as a thesis for the degree of Doctor of Medicine in the University of London, July 1922.

(Q. J. M., Jan., 1923.)

technique of the method used. (2) A statement as to the behaviour of the normal stomach when the same method is used (Bennett and Ryle). (3) Descriptions of the types of response to the test meal, the cases being grouped according to the anatomical findings at operation or autopsy. In some instances sub-groups have been introduced to deal with anatomical variations such as pyloric obstruction or hour-glass stomach. Under further sub-headings are grouped the various test meal findings. Tabulated analyses of all the cases are given (Tables I to XII), and eighteen test meal charts (Figs. 2 to 19) have been reproduced to illustrate certain cases. (4) A summary of the fractional test meal findings in disease.

Technique.

The apparatus employed comprised a stomach-tube, a 20 c.c. Record syringe, and a rack of twelve numbered test-tubes. The stomach-tube employed at the commencement of the investigation was that of Einhorn. It is of thin rubber, of about 8 mm. external circumference, and is marked transversely at 40 cm. to indicate the cardiac orifice, and at 57 cm. to indicate the pylorus. To one end is attached a hollow metal capsule perforated in several places. Early in this investigation it was sometimes found that strong suction exerted on an almost empty stomach caused damage to the gastric mucosa, and for this reason a modified stomach-tube devised by Ryle (2) has recently been employed. This has a bulbous extremity weighted with metal, and the perforations are in the rubber, so that the risk mentioned is eliminated. The test breakfast employed consists of thin gruel, made by adding a quart of water to two tablespoonfuls of fine oatmeal, boiling down slowly to a pint, and straining through muslin. The patient was starved from midnight, and at 9 a.m. the stomach-tube was passed by persuading him to swallow the bulbous end just like a pill, and the act of swallowing was continued until the pyloric mark almost reached the teeth. A sample of about 15 c.c. of the fasting stomach content was withdrawn by means of the syringe. In the course of the investigation the advantage of withdrawing and measuring the whole of the resting fluid was considered; but, since the method of taking only a sample was chosen in the beginning of the series it was adhered to for the sake of uniformity. Without withdrawing the tube the patient drank the pint of warm gruel; after which, at fifteen-minute intervals, samples of stomach content were aspirated, the tube remaining *in situ* for three hours. The patient could talk, read, or devote his attention towards any minor employment to pass the time. After withdrawal of each specimen, air was injected to empty the tube. Blocking of Ryle's tube seldom occurred; and when it did it was easily overcome by air-pressure, and there was rarely any difficulty in obtaining twelve specimens each of 10 or 15 c.c. At the end of three hours the tube was gently withdrawn, the patient being asked to swallow as it passed the level of the cricoid. The method was found always easy to apply and not too exacting in its demands on the patient.

In the laboratory the naked-eye appearance of each specimen and the amount

and colour of both sediment and supernatant fluid were noted. A rough estimate of the amount of each specimen and the presence or absence of bile, blood, and mucus were noted. Every specimen was titrated against standard alkali with dimethylaminoazobenzene as indicator for 'Töpfer acidity', and phenolphthalein for 'total acidity'. However, the Töpfer readings were only accepted as indicating free hydrochloric acid when the phloroglucin-vanillin test was positive. The acidity values are expressed in cubic centimetres of decinormal NaOH per 100 c.c. of stomach content. The emptying time of the stomach was estimated by the disappearance of the starch reaction as determined by the addition of a few drops of iodine solution to each tube.

For purposes of comparison, wherever possible, the Ewald test meal of tea and toast was given to the patient on the morning following the fractional meal. In such cases the Ewald reading will be found charted at the one-hour point. (See Figs. 2 to 19.)

I regret having missed the opportunity to estimate the total and mineral chlorides in this series, but such procedure is quite out of the scope of an individual, part-time worker.

Normal Gastric Function.

(From observations by Bennett and Ryle on 100 Healthy Males.)

[*Guy's Hosp. Rep.*, 1921, lxxi, No. 3, p. 317.]

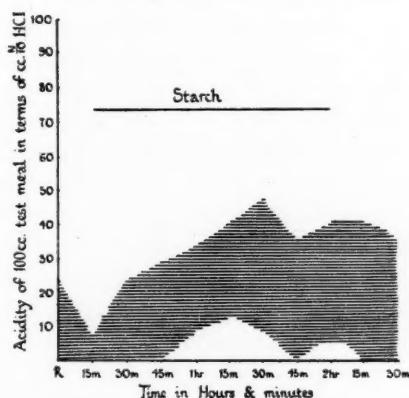


FIG. 1.

N.B.—The shaded area represents the limits of free HCl in 80 per cent. of healthy males.

Normal Gastric Function.

It will be well to point out here the behaviour of the normal stomach in response to the fractional test meal. In their recent work on the subject Bennett and Ryle (3) employed the technique just described in the investigation of gastric function in 100 healthy males. They drew up a chart representing the limits of the secretion of free hydrochloric acid in 80 per cent. of healthy males. This chart is reproduced in Fig. 1, and is taken, throughout this communication, to represent the limits of normal gastric secretion.

TABLE I. *Chronic Ulcer of Duodenum. 15 Cases.*

Case No.	Ease or difficulty with which Specimens were withdrawn.	Description of Specimens.	Number of Tubes containing			Type of Curve.	Rate of emptying in hrs. and mins.	Fractional Test Meal.				Ewald Test Meal	
			Bile.	Blood.	Mucus.			Resting Fluid.		Maximum.		Free HCl.	Total Acidity.
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.		
3	—	—	0	0	0	Sharp rise.	2.30	0	8	52	70	44	66
72	—	—	5	0	0	Marked plateau Sharp rise. Plateau	1.30	0	33	80	90	66	78
73 a	Ease	Clear, colourless	0	0	0	Sharp rise.	2.15	27	37	66	78	74	98
87	Ease	Clear, colourless	1	0	0	Marked plateau Sharp rise.	1.30	0	22	73	87	30	48
198	Ease	Opalescent	0	0	0	Marked plateau Sharp rise.	2.15	19	31	68	78	52	71
134	Great ease	Clear, colourless	7	0	0	Plateau Sharp rise.	1.30	73	83	77	87	41	73
156	Ease	Clear, colourless	1	4	0	Plateau Sharp rise.	2.30	38	53	75	87	55	69
169	Ease	Clean deposits. Clear fluid	1	0	4	Plateau Sharp rise.	2.30	28	59	52	64	46	60
243	Ease	Opalescent	3	0	1	Sharp rise. Plateau	2.0	37	54	106	112	—	—
90	Great ease	Clean deposits. Transparent fluid	1	0	0	Climbing type	2.15	58	70	68	81	63	87
122	Ease	Small deposits. Clear fluid	0	0	0	Climbing type	1.30	32	46	60	85	37	67
214	Fair ease	Much deposit. Clear fluid	2	0	0	Climbing type	2.45	28	40	49	75	0	32
240	Ease	Large deposits. Dirty fluid	0	0	0	Climbing type	2.45	67	78	52	78	—	—
32	Fair ease	Large deposits. Dirty fluid	3	0	2	Low climbing type	2.45	0	31	35	61	—	—
203	Ease	Large deposits. Dirty fluid	1	0	7	Almost complete achlorhydria	2.45	23	35	23	35	0	44

Acute Ulcer of Duodenum. 1 Case.

168	Ease	Turbid	3	0	0	Delayed rise.	2.45	34	46	77	86	—	—
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1. *Chronic Ulcer of Duodenum.*

The findings here are more constant than in any other type. Analysis of sixteen cases shows a very copious secretion of fluid throughout the whole digestive cycle. Thus, in twelve cases the resting fluid was easily obtained and was found to be a clear, colourless, or slightly opalescent fluid devoid of deposit. Subsequent specimens were of strikingly clean appearance, and often, after the stomach had emptied, the fluid obtained was like water in appearance, with perhaps a few flecks of floating mucoid material. In only five cases was bile completely absent; in the remainder it was usual to find it, either occurring in odd specimens, or else appearing for about forty-five minutes immediately following the emptying of the stomach. Case 156 is the only one where blood was discovered, and here all specimens after the second hour were turbid and deeply stained with dark blood. Clinically, this immediately preceded an attack of melaena. Mucus appeared only in four instances, a finding which harmonizes with the clean, copious, thin, clear fluid characteristic of this type.

In considering the actual type of curve, the cases fall into two groups, those with obstruction and those without.

Group I. Cases without obstruction. This group is represented by the first nine cases (see Table I). Here the average history was about five to ten years, and the usual finding was a small, chronic, non-adherent ulcer with hyperaemic stippling of the peritoneum, but very little induration, and with only slight scarring. There was no deformity and no stenosis of the lumen of the duodenum.

In all of this group of cases the test meal curve is remarkably constant (see Fig. 2). It commences with a resting fluid where the average free HCl is 26 (0.09 per cent.) and total acidity 43. On administration of the meal it falls in most cases to zero, but the free HCl may remain always at a level above 20 (0.07 per cent.). Within thirty minutes of taking the meal there is a very steep rise, attaining a maximum usually at the one-hour point, the average of which is free HCl 68 (0.25 per cent.) and total acidity 78. The curve is then continued as a plateau, which usually remains approximately horizontal or shows a slight gradual rise or fall. Further, it is noteworthy that the curves for free and total acidity remain very close together throughout. In this group the average reading for the Ewald meal, taken at one hour, is lower by about 13 per cent. than that of the maximum fractional value, namely, free HCl 51 (0.19 per cent.) and total acidity 70. Concerning the rate of emptying, it will be seen that in eight out of the nine cases starch has disappeared before the completion of the test. In fact, the stomach is often empty in one hour thirty minutes. This corresponds with the usual radiographic finding of a small hyperperistaltic stomach with rapid emptying.

Analysis of the opaque meal findings shows that in the above nine cases there was direct evidence of ulcer in three cases, indirect evidence in three cases, and no evidence of organic disease in three cases.

Group II. Cases with obstruction. In this group are the remaining six

cases (see Table I). Here the average history was twenty to twenty-five years, and the usual finding was a large indurated ulcer with scarred deformity and stenosis of the first part of the duodenum. In some of the cases it was adherent posteriorly to the pancreas, in others it was freely mobile and situated anteriorly.

In this group the appearance of the test meal departs somewhat from the description given above. It shows evidence of the obstruction in the delayed emptying of the stomach, leaving large deposits of dirty porridge with a little turbid supernatant fluid. The specimens, as before, are all easily obtained, but the resting fluid is no longer opalescent and devoid of deposit, but contains a dirty brown mucoid deposit and turbid supernatant fluid. The curve (see Fig. 3) commences with a higher resting fluid than in the first group, the average

Chronic Ulcer of Duodenum. Group I.

Case 73 a. ♂ 27. 14 April 1921.

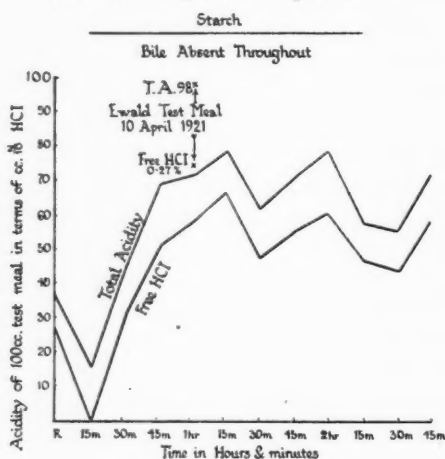


FIG. 2.

Description.—Specimens withdrawn with ease. All deposits very clean. Clear, colourless, supernatant fluid. No mucus. Fluid like water in last three specimens.

figure being free HCl 35 (0.13 per cent.) and total acidity 50. Immediately after the meal it falls to zero, and then assumes the 'climbing type', gradually and uniformly rising to reach a maximum at the two-hour point. The average figure at this point is free HCl 50 (0.18 per cent.) and total acidity 69. In this group the average reading for the Ewald meal, taken at one hour, is lower by about 32 per cent. than that of the maximum fractional value, namely, free HCl 25 (0.09 per cent.) and total acidity 59. It is to be noted that the curves for free and total acidity are usually much more widely separated than in Group I, though they still run parallel. Tests for starch showed that porridge usually remained in the stomach at the end of the third hour.

The majority of the opaque meal reports showed hypotony and delay, and

Chronic Ulcer of Duodenum. Group II.

Case 240. ♂ 42. 23 February 1922.

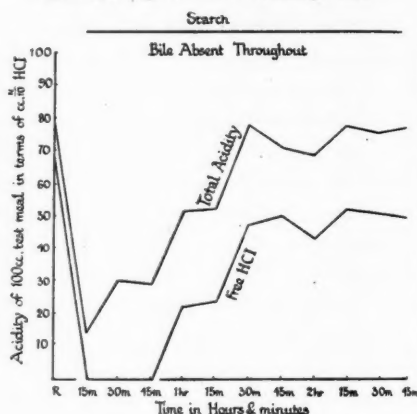


FIG. 3.

Description.—Specimens withdrawn with ease. Resting fluid turbid, brown, opalescent, with dirty mucoid deposit. Large deposits of curdled dirty brown porridge with a little brown opalescent supernatant fluid in remainder. No mucus.

in only one of the six cases was there no evidence, direct nor indirect, of organic lesion.

There is one curve worthy of special mention, because it bears no resemblance to the other fifteen.

Case 203. This was a man of 39, giving a history of two long attacks of pain late after food, one ten years, the other six years ago. Between these dates he had been perfectly well, and since the latter he had had no pain but three severe attacks of melaena, the last three months before. The test meal showed almost complete achlorhydria. The specimens were easily obtained, and consisted throughout of large amounts of porridge and mucus with turbid supernatant fluid. The resting fluid was bile-stained and showed free HCl 23 (0.08 per cent.) and total acidity 35. These points were not subsequently reached during the three hours, and at only two points did free HCl again appear. This condition is frequently observed after haematemesis or melaena, the presumption being that the gastric secretion diminishes with haemorrhage. If this be so, then apparently the blood picture often recovers before the gastric secretion. Thus, in this case the red blood corpuscles were 6,540,000 per c.mm., and the haemoglobin 100 per cent., though the patient, after his last attack of melaena, remained blanched for several weeks. Unfortunately, there is no record of the previous blood condition nor of any previous gastric analysis. However, it has been established in parallel cases that a prolonged secondary anaemia due to repeated haemorrhages may produce such permanent changes in the gastric mucous membrane that free HCl remains absent from the gastric secretion after the blood condition has become normal. Thus Panton and Tidy (4) quote a case under the care of Dr. Hutchison of a patient 'who had suffered from rectal haemorrhage for sixteen years. When admitted to hospital his Ewald test meal showed absence of HCl and a total acidity of 10. His red cells numbered 3,000,000 per c.mm., and his haemoglobin was 30 per cent. Nine months after a radical cure for haemorrhoids, though greatly improved in health, he still complained of dyspepsia; his blood condition had become normal, but there was still an absence of free HCl in his gastric juice.'

2. *Acute Ulcer of Duodenum.*

Only one case of acute duodenal ulcer was investigated.

Case 168. This was a man of 68, giving a history of pain recurring in short attacks of four days, over a period of five years. In the intervals there was perfect freedom up to three months. The pain was not severe, was referred to the umbilicus, occurred late after food which sometimes relieved it, and was never associated with vomiting. The test meal finding was indistinguishable from that described in cases of chronic duodenal ulcer without obstruction (see Fig. 2). At operation, no thickening could be felt, but on the anterior aspect of the first part of the duodenum there was a small area of hyperaemic stippling of the peritoneum 6 mm. across. On exploring the duodenum there was found, immediately deep to this, a non-indurated erosion of the mucosa (2 mm. by 1 mm.).

3. *Chronic Ulcer of Pyloric End of Stomach.*

Under this heading I have included also those ulcers which may have arisen in the duodenum and crossed the pyloric sphincter to involve the stomach. The findings, though less consistent than in the case of duodenal ulcer, are still fairly reliable. The cases fall roughly into three groups, namely:

TABLE II. *Chronic Ulcer of Pyloric End of Stomach. 15 Cases.*

Case No.	Ease or difficulty with which Specimens were withdrawn.	Description of Specimens.	Number of Specimens containing			Type of Curve.	Time of emptying in hrs. and mins.	Fractional Test Meal.				Ewald Test Meal.	
			Bile.	Blood.	Mucus.			Resting Fluid.		Maximum.		Free HCl.	Total Acidity.
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.		
99	Ease	Clean deposits. Turbid fluid	0	0	0	Climbing type	2.45	48	66	40	70	44	56
248	Great ease	Much deposit. Opalescent fluid	3	0	0	Climbing type. Falls off	2.45	20	30	59	70	78	89
231	Ease	Much deposit. Turbid fluid	6	0	3	Climbing type	2.45	47	72	61	73	61	77
183	Ease	Much deposit. Translucent fluid	5	0	1	Climbing type. Falls off	2.45	0	15	42	64	34	59
29	Ease	Dirty deposits. Turbid fluid	1	0	0	Low climbing type	2.45	15	28	26	44	0	35
22	Great ease	Large deposits. Opalescent fluid	0	0	0	High climbing type	2.45	76	106	76	106	46	76
157	Great ease	Clean deposits. Transparent fluid	1	0	0	Uniform rise and fall	2.30	0	16	47	65	49	63
38	Ease. Starch	Much deposit. Turbid fluid	1	0	0	Delayed sharp rise. Plateau off	2.45	20	52	46	60	22	44
255	Fair ease	Clean deposits. Translucent fluid	1	4	0	Sharp rise. Falls off	2.45	0	29	75	88	—	—
175	Ease	Clean deposits. Transparent fluid	7	0	0	Sharp rise	2.45	72	79	72	79	—	—
152	Ease	Clean deposits. Transparent fluid	2	0	0	Sharp rise. Plateau	1.15	0	35	78	89	55	73
41	Ease. Starch	Dirty deposits. Brown. Offensive	0	0	0	Slow falling	2.45	50	76	50	76	41	61
221	Ease	Large deposits. Turbid fluid	0	0	0	Uniform rise and fall	2.45	16	38	27	52	22	37
252	Ease	Clean deposits. Opalescent fluid	0	0	0	Sharp rise. Falls off	2.45	0	10	40	73	42	59
220	Ease	Clean deposits. Cloudy fluid	9	0	0	Sharp rise. Low plateau	2.45	37	45	37	45	—	—

(i) Those with a short history of three or four years, where a small ulcer, up to 0.5 cm. across, was found, and where stenosis was absent.

(ii) Those with a history of ten to twenty years, where a large indurated ulcer, up to 2 cm. across, perhaps with a border 0.5 cm. thick, had caused scarring and stenosis of the pylorus.

(iii) Those with a past history of ulcer, where the pain had lost its periodicity or had disappeared entirely, the chief complaint being of large foul vomits. Here the surgical finding was a large dilated and hypertrophied stomach with pyloric obstruction from a scar showing no induration, no hyperaemic stippling of the peritoneum, nor any other sign of active ulceration.

The fractional test meals coincide fairly well with these case groupings, except for the fact that pyloric stenosis, unless it be extreme, shows few manifestations on the test meal chart. Hence Groups I and II are very similar for average cases.

Group I. Cases without obstruction. Of the fifteen cases recorded (see Table II), seven were found at operation to have produced no stenosis; and of these seven five were of the 'climbing type' illustrated in Fig. 4. The specimens were obtained with ease, the deposits of porridge were usually clean and copious, and the supernatant fluid turbid or opalescent. Bile was usually present at some time or another, blood appeared in small amounts in one case only, and mucus was invariably absent. The resting fluid usually showed a higher reading than that in the particular case depicted, the average for this group being free HCl 27 (0.10 per cent.) and total acidity 45. The curve shows a gradual rise attaining, at about the two-hour point, an average of free HCl 48 (0.18 per cent.) and total acidity 64. After this point it drops somewhat, usually about 15 points, and in one case it reached the base line. In this group the average reading for the Ewald meal, taken at one hour, is lower by about 41 per cent. than that of the maximum fractional value, namely, free HCl 25 (0.09 per cent.) and total acidity 48. Concerning the rate of emptying, in every case starch remained in the stomach at the completion of the test.

Of the remaining two cases where no obstruction was found, the first was of similar configuration to those described above, but much lower, viz. 'low climbing type'. The patient was wasted and much enfeebled from starvation and vomiting, and the low acidity was doubtless due to a secondary gastritis consequent on the presence of the ulcer.

The other case is interesting as being the youngest woman with a chronic ulcer in the whole series of cases:

Case 255. She was a domestic servant of 25, with a typical chronic ulcer history dating back three years. At operation was found a radiating scar (1.5 cm. diameter) astride the pyloric vein. There was puckering and slight hyperaemic stippling of the peritoneum to be seen, but very little induration to be felt. Exactly opposite, on the posterior wall of the pylorus, was a small apposition ulcer the size of a pea, too small for a crater to be made out. The pylorus was somewhat indented from scarring, but there was no marked obstruction, and no hypertrophy of the stomach. The test meal showed clean deposits and translucent fluid, with a curve rising abruptly to a very high level (T.A. 88), and passing on

to a plateau with a considerable drop in the last hour. Starch was found at the end of the test. Hence, except for the delayed emptying, the finding was similar to that of uncomplicated duodenal ulcer.

Group II. Cases with obstruction. Six cases (see Table II) were found to have pyloric ulcer causing stenosis; and, of these, three showed findings identical with those described above for pyloric ulcer without stenosis.

The fourth case showed a finding identical with that of uncomplicated duodenal ulcer.

*Chronic Ulcer of Pyloric End of Stomach.
Group I.*

Case 183. ♂ 27. 31 October 1921.

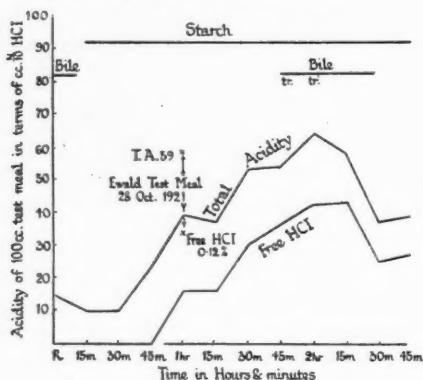


FIG. 4.

Description.—Specimens withdrawn with ease, except the last. Deposits clean. Full volume of porridge up to two hours. Translucent supernatant fluid. No mucus.

*Chronic Ulcer of Pyloric End of Stomach.
Group II.*

Case 252. ♂ 49. 7 March 1922.

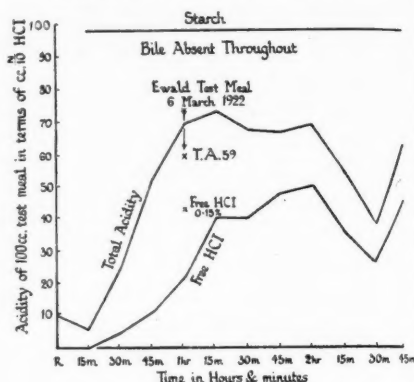


FIG. 5.

Description.—Specimens withdrawn with ease. Clean deposits. Full volume of porridge to one hour. Supernatant fluid opalescent. No mucus.

The fifth case (Fig. 5), though an exception, has been reproduced here to show the gradation between this group and the next. It is from a patient where considerable stenosis of the pylorus had been brought about by a large chronic ulcer (1.5 cm. diameter), situated on the posterior aspect of the lesser curve, in the pyloric antrum. The acidity of the resting fluid is low; the curve rises abruptly to a high level, which is maintained as a plateau during the second hour, but falls off during the third. The wide interval between the curves of free and total acidity, the turbidity of the fluid, and the delayed emptying combine to suggest a degree of obstruction greater than that found in the first four cases of this group.

The sixth case (22) shows marked pyloric obstruction in a hypersecretory stomach. When the tube was passed, large quantities of thin, opalescent resting fluid passed from it in a rapid stream. There were large curdled deposits in every tube, which remained two-thirds of the total volume throughout. All the specimens had the curious, rancid odour of butyric acid. At the end of the test the stomach was still pouring out copious quantities of thin fluid. The configuration of

the curve is similar to that of Fig. 3, but the readings are at a higher level, reaching total acidity 108. There is a very wide gap between the curves of free and total acidity, reaching 44 points in places.

Group III. Cases with great dilatation of the stomach. Two cases were found to have a huge, dilated, hypertrophied stomach with a healed scar at the pylorus.

One of these is described here:

Case 41. This was a man of 52 giving a history of pyloric ulcer twelve years before with definite remissions, but for the past three years he had been troubled with offensive flatulence, and with large foul vomits, containing cellulose residues of some days before. More recently he had had an attack of tetany. His stomach was visible low down in the pelvis, being outlined by an extensive zone of visible peristalsis and by a succussion splash. The test meal chart (see Fig. 6) shows the curve of total acidity widely separated from that of free HCl, each running at a high level, dropping very gradually, and never approaching the zero line closer than a point indicating free HCl 28. The resting fluid shows an acidity considerably higher than that attained at any subsequent point in the curve, namely, free HCl 50 (0.18 per cent.) and total acidity 76. The severity of the stasis and obstruction is well indicated by the presence in the resting fluid of a large volume of dirty, brownish deposit, containing starch and delayed cellulose residues.

Chronic Ulcer of Pyloric End of Stomach. Group III.

Case 41. ♂ 52. 29 November 1920.

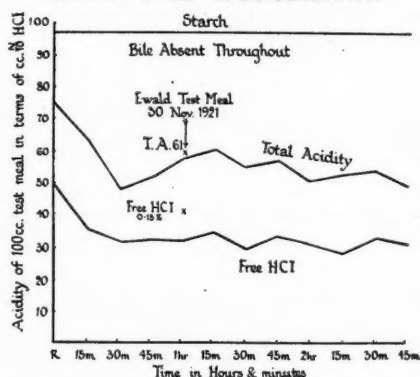


FIG. 6.

Description.—Dirty brownish solid deposit comprised two-thirds of the total volume in each specimen, including the resting fluid. Cellulose particles not administered were found. The supernatant fluid was clear.

4. Chronic Ulcer of Body of Stomach.

In this group the surgical findings fall into two categories. The first, and commoner, is of a small ulcer about 0.5 cm. across on the anterior aspect of the body of the stomach, situated adjacent to the lesser curve, either at about its mid-point, or else higher up towards the oesophagus. There is usually hyperaemic stippling of the peritoneum, scarring, induration of the gastro-hepatic omentum, and chronic inflammatory enlargement of glands. The history averages four or five years.

TABLE III. *Chronic Ulcer of Body of Stomach. 20 Cases.*

Case No.	Ease or difficulty with which Specimens were withdrawn.	Description of Specimens.	Number of Tubes containing			Type of Curve.	Rate of emptying in hrs. and mins.	Fractional Test Meal.				Ewald Test Meal.	
			Bile.	Blood.	Mucus.			Resting Fluid.		Maximum.		Free HCl.	Total Acidity.
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.		
262	Fair ease	Clean deposits. Opalescent fluid	2	3	1	Peak at 45 mins. Falls off	2.45	0	15	35	52	28	45
253	Ease	Clean deposits. Opalescent fluid	0	0	1	Uniform rise and fall	2.45	0	8	36	56	75	88
191	Fair ease	Dirty deposits. Macroscopic blood	0	12	1	Uniform rise and fall	2.0	0	18	27	41	55	77
6	Fair ease	Dirty deposits. Turbid fluid	2	0	0	Falling	2.30	0	40	0	17	41	70
19	—	—	5	0	1	Almost complete achlorhydria	2.0	0	7	0	16	0	20
100	Ease	Clean deposits. Turbid fluid	6	0	0	Very low plateau	2.15	0	14	0	33	28	44
125	Ease	Slight deposits. Clear fluid	1	1	3	Uniform rise and fall	2.30	0	25	32	53	69	99
145	Ease	Clean deposits. Transparent fluid	0	0	1	Complete achlorhydria	2.0	0	10	0	9	0	16
241	Fair ease	Slight deposits. Transparent fluid	1	0	0	Complete achlorhydria	1.30	0	5	0	21	—	—
39	—	Clean deposits. Opalescent fluid	6	0	0	Low hypochlorhydria	1.30	0	19	19	44	38	57
178	Ease	Clean deposits. Opalescent fluid	0	0	4	Uniform rise and fall	2.30	0	16	45	53	52	60
176	Ease	Clean deposits. Clear fluid	8	0	1	Uniform rise and fall	2.45	16	29	52	63	0	46
155	Ease	Clean deposits. Translucent fluid	0	0	1	Uniform rise and fall	2.45	18	38	44	59	0	37
56	—	—	1	0	0	Uniform rise and fall	2.15	42	56	63	77	41	63
256	Ease	Clean deposits. Transparent fluid	0	3	1	Sharp rise. Plateau	2.45	0	10	59	68	40	56
234	Fair ease	Dirty deposits. Turbid fluid	0	0	1	Climbing type	2.45	21	31	58	64	—	—
187	Great ease	Copious deposits. Translucent fluid	0	0	0	Delayed sharp climb	2.45	47	57	65	92	60	79
173	Ease	Clean deposits. Opalescent fluid	0	0	0	Climbing type	2.15	20	42	73	83	40	57
2	—	—	3	0	0	Climbing type	2.30	0	30	56	62	0	34
15	—	Copious deposits	0	0	0	Climbing type	2.45	0	13	38	58	38	56

Of twenty cases recorded, eleven conform to this type. In the twelfth case of anterior ulcer there was a history of twenty years, and a hard irregular mass was found astride the lesser curve. This was suspected of being carcinoma, but sections showed only chronic inflammatory fibrosis with dense infiltration by eosinophil leucocytes and plasma cells.

The remaining eight cases had an average history of ten or fifteen years, and showed thick-walled ulcers, often 1.5 cm. across, on the posterior aspect of the body of the stomach, adherent to the pancreas.

It was possible only rarely to determine at operation the presence of pylorospasm.

A. *Ulcers situated posteriorly.* Analysis of the test meal findings reveals the fact that there is no perfect accordance with the above case-groupings. However, six out of eight of the cases of posterior ulcer conform to the type shown in Fig. 8. The specimens are easily withdrawn, the deposits usually clean, and the supernatant fluid clear. Bile is present in half the cases. In three cases, also, blood was detected, and in one of these it was present in large amounts throughout the whole test. The stomach may empty in $2\frac{1}{2}$ hours, but usually starch remains at the end of the test. The curve commences with a low resting fluid, and shows a uniform rise and fall. The maximum point is at one hour thirty minutes, and its average height is free HCl 37 (0.14 per cent.) and total acidity 56. Unlike that of pyloric ulcer the curve drops to the zero line during the third hour.

B. *Ulcers situated anteriorly.* Of anterior ulcers twelve cases are recorded, and they fall into three groups: *Group I.* This group comprises three cases which conform to the type described above. *Group II.* This group comprises five cases which conform to the type shown in Fig. 7, where the curve is of similar configuration to that described for pyloric ulcer, namely the 'climbing type'. Further, the average figures show that the maximum levels are almost identical for both types of ulcer. There are, however, two minor differences:

(i) The acidity of the resting fluid is lower in the case of ulcer of the body of the stomach, the average being free HCl absent, and total acidity 28.

(ii) The terminal drop seen in the case of pyloric ulcer is usually absent.

In this type starch usually remains in the stomach at the end of the test. Bile was found only in two cases of this group, and mucus only in one case. In contradistinction to ulcers of the posterior group blood never appeared.

Group III. This group comprises four cases which show complete or almost complete achlorhydria. These belong to a somewhat isolated clinical type occurring usually in men over forty-five years of age with a short history covering only two or three years, and often devoid of definite periodicity. At operation a small ulcer was discovered, usually at the central point of the lesser curve, and it was frequently so small as to be evident only to palpation. The charts, as in most cases of achlorhydria, indicate a rapid emptying of the stomach in $1\frac{1}{2}$ or 2 hours. The behaviour of the secretion, however, is very unlike that in cases, for instance, of pernicious anaemia and cirrhosis of the liver, for there is an increase

of the hypo-acid fluid. Thus specimens of copious, clean, opalescent fluid with little mucus were obtained with ease during the whole of three hours.

Taking an average of all ulcers of the body of the stomach grouped together, the maximum readings for free HCl and total acidity are practically identical with the corresponding findings for the Ewald meal taken at one hour in the same series of cases.

Chronic Ulcer of Body of Stomach.—Group I.

Case 234. ♂ 50. 13 February 1922.

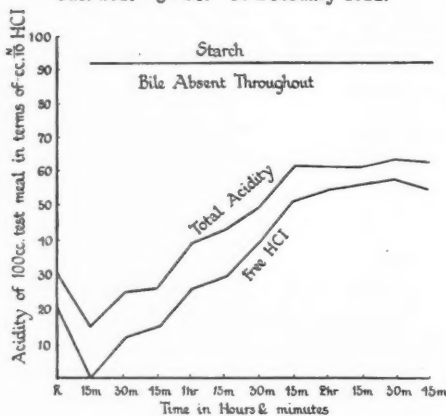


FIG. 7.

Description.—Specimens withdrawn with a little difficulty. Deposit clean. Full volume of porridge up to 2 hours. Turbid supernatant fluid. No mucus.

Chronic Ulcer of Body of Stomach.—Group II.

Case 178 ♀ 53. 26 October 1921.

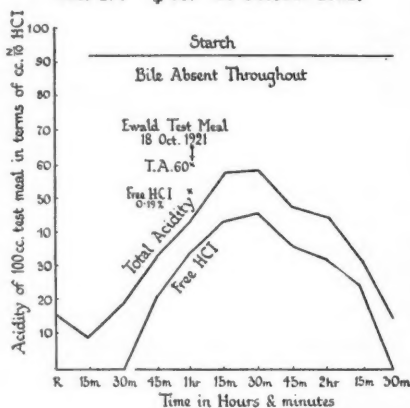


FIG. 8.

Description.—Specimens withdrawn with ease. Clean deposits; porridge visible up to 2 hours. Transparent supernatant fluid with mucoid flecks.

The phenomenon of pylorospasm would seem to influence the test meal finding in cases with ulcer of the body of the stomach; but, owing to its intermittent character, and to the difficulty of demonstrating it at operation, its existence in any particular case must remain a matter of conjecture. Clinically the time relation of the pain to food has some bearing on the question. Thus, in this series, 40 per cent of patients complained of pain at times varying from fifteen minutes to one hour after food, 35 per cent. of pain one and a half to two hours after food, whereas 25 per cent. had two distinct types of pain, the first occurring early, and the second late, after food.

The relation of such symptomatology to the test meal charts may be sought in the type of curve. Selecting, in this series, those cases where pylorospasm is suggested by delayed emptying, associated with the climbing type of curve, it is found that, of seven such cases, five complained of pain late after food. Of the remaining seven with pain late after food, the chart offered no suggestion of pylorospasm, the curve dropped to the base line in the third hour, and marked delay was absent. The difference between the two groups possibly rests in the fact that, though the phenomenon may occur in many cases, it is only actually present during the test meal examination in few. Now, this is an important

TABLE IV. *Hour-glass Stomach. 5 Cases.*

Case No.	Ease or difficulty with which Specimens were withdrawn.	Description of Specimens.	Number of Specimens containing			Type of Curve.	Time of emptying in hrs. and mins.	Fractional Test Meal.				Ewald Test Meal.	
			Bile.	Blood.	Mucus.			Resting Fluid.		Maximum.		Free HCl.	Total Acidity.
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.		
19	—	—	5	0	1	Low hypochlorhydria	2.0	0	7	9	38	0	20
242	Difficulty	Clean. Opalescent fluid	0	0	0	Low hypochlorhydria	1.0	0	9	0	26	38	52
62	Ease	Transparent fluid	0	0	5	Uniform rise and fall	1.0	0	8	30	46	49	62
251	Ease	Clean deposits. Opalescent fluid	0	1	0	Sharp rise. Low plateau	2.45	0	6	48	57	53	76
164	Ease	Clean deposits. Transparent fluid	0	0	0	Climbing type	2.45	86	104	86	104	22	42

Visceroptosis. 7 Cases.

34	—	—	8	0	0	Complete achlorhydria	2.45	0	7	0	12	0	9
123	Fair ease	Slight deposits. Opalescent fluid	0	0	0	Complete achlorhydria	1.15	0	19	0	23	0	23
200	Great difficulty	Translucent	4	0	1	Complete achlorhydria	0.30	0	4	0	6	19	36
245	Ease	Clean deposits. Opalescent fluid	1	0	0	Complete achlorhydria	2.15	0	6	0	19	—	—
186	Ease	Dirty deposits. Cloudy fluid	1	0	8	Complete achlorhydria	0.45	0	6	0	9	0	8
174	Fair ease	Clean deposits. Turbid fluid	4	0	0	Uniform rise and fall	2.45	—	—	25	47	—	—
61	Ease	Large deposits. Turbid fluid	5	0	0	Climbing type	2.45	22	56	31	59	38	59

group of cases from the point of view of diagnosis; for, though the relation of the pain to food suggests duodenal or pyloric ulcer, the test meal chart completely negatives this diagnosis.

5. Hour-glass Stomach.

Five cases are recorded, all in women of about 40 years of age. The history extends usually over twenty-five years. There are two very distinct groups according to whether or not pyloric stenosis exists as a complication.

Group I. Uncomplicated cases. In this group are three cases, all with large chronic ulcer of the body of the stomach, where scarring has caused definite biloculation. Two of the ulcers penetrated the pancreas, and one was situated anteriorly. There was no other abdominal lesion. The test meal findings here were almost identical with that group of ulcers just described in which achlorhydria was found. Thus, there was copious, clean, opalescent fluid with very little deposit, though in two cases considerable quantities of mucus appeared. The emptying rate is more rapid than in uncomplicated ulcer, so much so that starch may disappear in one hour. However, this probably represents only the passage of the meal from the proximal to the distal loculus. The curve shows a slight uniform rise and fall, the average maximum points being free HCl 20 (0.07 per cent.) and total acidity 37. The average Ewald reading taken at one hour in the same series is free HCl 29 (0.10 per cent.) and total acidity 45.

Group II. Cases complicated by pyloric stenosis. In the second group are included two cases where multiple chronic stenosing ulcers were found, causing both biloculation and pyloric stenosis. In addition to ulcer of the body of the stomach and ulcer of the pylorus there were other abdominal lesions, namely, in one case chronic apposition ulcers of the duodenum, and, in the other, profound visceroptosis with chronic appendicitis. Referring to the curves it is found that both are of the climbing type with delayed emptying of starch. In one the resting fluid shows a free HCl of 86 (0.31 per cent.) and a total acidity of 104; in the other the resting fluid shows achlorhydria.

6. Cases examined after Operation.

Forty-three cases, including ulcer of the duodenum, pylorus, and body of the stomach, have been examined by the fractional method at varying intervals after operation. The test meal was usually given during the third week after operation, but cases have been examined from three months to eight years later. The type of operation can be classified as:

1. Simple excision of ulcer (two cases).
2. Pyloroplasty (one case).
3. Gastro-jejunostomy:
 - (a) without occlusion of the pylorus (nineteen cases);

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(b) where the pylorus was occluded by a running mattress-suture of silk (twenty-one cases).

In this group the actual method of dealing with the ulcer includes: (a) leaving it untouched, (b) submucous resection of ulcer, (c) wide wedge resection of stomach, (d) invagination of ulcer by purse-string suture, (e) cauterization of ulcer with invagination, (f) partial gastrectomy.

TABLE V. *Duodenal Ulcer after Operation. 13 Cases.*

I. After Posterior Gastro-jejunostomy with Occlusion of Pylorus.

Case No.	Before Operation.				After Operation.					'Follow Through.'	
	Type of Curve.	Empty-ing Rate.	Free HCl.	Total Acidity.	Type of Curve.	Empty-ing Rate.	No. of Tubes with Bile.	Free HCl.	Total Acidity.		
134	Sharp rise. Marked plateau	1.30	77	87	Sharp rise. Marked plateau	1.15	12	71	82	Well on discharge	
214	Climbing. Falls off	2.45	49	75	Climbing. Falls off	1.15	12	30	56	Well on discharge	
198	Sharp rise. Plateau	2.15	68	78	Complete achlor-hydrria	1.0	10	0	26	Remains 4 months	well
203	Almost complete achlor-hydrria	2.45	23	35	Low climb-type	1.0	11	44	54	Remains 4 months	well
232	—	—	59	70	Complete achlor-hydrria	2.45	12	0	15	Recurrent ulcer	

II. After Posterior Gastro-jejunostomy without Occlusion of Pylorus.

3	Sharp rise. Marked plateau	2.30	52	70	Complete achlor-hydrria	2.0	12	0	16	Remains 14 months	well
73a	Sharp rise. Marked plateau	2.15	66	78	Complete achlor-hydrria	1.15	12	0	26	Pain after 3 months	
90	Climbing type	2.15	68	81	High climbing type	2.45	6	75	88	Remains 3 months	well
243	Sharp rise. Rising plateau	2.0	106	112	High climbing type	2.15	12	95	100	Well on discharge	
117	—	—	35	49	Uniform rise and fall	1.15	9	38	52	Pain after 15 months	
263	—	—	38	55	Sharp rise and fall	2.30	10	70	83	Pain after 12 months	
181	—	—	—	—	Delayed rise and fall	2.30	7	49	59	Pain after 1 month	

III. After Pyloroplasty.

168	Sharp rise. Plateau	2.55	77	86	Sharp rise. Plateau	2.15	1	69	78	Pain after 3 months	
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Group I. After simple excision of ulcer. Two cases are recorded in this group (see Table VII).

Case 267. This was a man of 26, who, previously to his original operation, had shown an Ewald reading of free HCl 38 (0.14 per cent.) and total acidity 51. Submucous resection of a small non-adherent ulcer of the body of the

stomach was performed, and three weeks later he showed a low hypochlorhydria with the maximum acidity at the two-hour point, viz. free HCl 21 (0.08 per cent.) and total acidity 37. He was well for six months, and then had pain and severe haematemesis. On exploration a large recurrent ulcer, 2.5 cm. across, was found arising on the posterior margin of the lesser curve, and penetrating the pancreas.

TABLE VI. *Pyloric Ulcer after Operation. 13 Cases.*I. *After Posterior Gastro-jejunostomy with Occlusion of Pylorus.*

Case No	Before Operation.				After Operation.					'Follow Through.'	
	Type of Curve.	Emptying Rate.	Free HCl.	Total Acidity.	Type of Curve.	Emptying Rate.	No. of Tubes with Bile.	Free HCl.	Total Acidity.		
231	Climbing type	2.45	61	73	Sharp rise. Secondary rise	1.30	9	85	91	Remains 4 weeks	well
183	Climbing type	2.45	42	64	Sharp secondary rise	1.0	12	51	69	Well on discharge	
22	High climbing type	2.45	76	106	Sharp rise and fall	2.15	8	60	80	Remains 3 months	well
157	Uniform rise and fall	2.30	47	65	Delayed climbing type	2.45	11	55	62	Well on discharge	
255	Sharp rise. Falls off	2.45	75	88	Sharp rise. Falls off.	2.45	12	70	76	Well on discharge	
152	Sharp rise. Plateau	1.15	78	89	Complete achlorhydria	2.45	12	0	52	Well on discharge	
221	Uniform rise and fall	2.45	27	52	Complete achlorhydria	1.45	11	0	20	Remains 6 months	well
175	Sharp rise. Plateau	2.45	72	79	Complete achlorhydria	2.45	9	0	29	Nausea and discomfort	
248	Climbing type. Falls off	2.45	59	70	Almost complete achlorhydria	2.15	11	19	30	Remains 3 weeks	well
250	—	—	—	—	Sharp rise. Falls off.	2.0	12	49	59	Gastro-jejunal ulcer	

II. *After Posterior Gastro-jejunostomy without Occlusion of Pylorus.*

41	Slow, falling	2.45	50	76	Slight rise and fall	2.15	12	32	45	Remains 3 months	well
99	Climbing type	2.45	40	70	Sharp rise and fall	1.30	10	47	58	Well on discharge	
105	—	—	38	57	Sharp rise and fall	1.15	12	48	64	Gastro-jejunal ulcer	

Case 101. This was a man of 34, who, before operation, had shown an Ewald reading of free HCl 25 (0.09 per cent.) and total acidity 40. A large ulcer was removed with a portion of adherent pancreas. Three weeks after this he showed complete achlorhydria, with a maximum total acidity of 13. Subsequently he was well four months, and then had repeated severe haematemesis, when a third test meal showed complete achlorhydria again.

Group II. After pyloroplasty. There is only one case in this group.

Case 168. This was a man of 68, where a small erosion of the mucous membrane was found, opposite an area of hyperaemic stippling of the peritoneum,

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TABLE VII. *Ulcer of Body of Stomach after Operation. 17 Cases.*

I. *After Partial Gastrectomy.*

Case No.	Before Operation.				After Operation.					'Follow Through.'
	Type of Curve.	Emptying Rate.	Free HCl.	Total Acidity.	Type of Curve.	Emptying Rate.	No. of Tubes with Bile.	Free HCl.	Total Acidity.	
256	Sharp rise. Plateau	2.45	59	68	Complete achlor-hydrria	0.45	11	0	12	Well on discharge
251	Sharp rise. Plateau	2.45	48	57	Complete achlor-hydrria	0	12	0	30	Well on discharge
207	Low climbing type	2.45	46	58	Complete achlor-hydrria	0.30	12	0	26	Pain since operation
98	—	—	—	—	Sharp rise and fall	0.30	10	59	70	Pain after 3 years

II. *After Resection of Ulcer, Gastro-jejunostomy, and Occlusion of Pylorus.*

176	Uniform rise and fall	2.45	52	63	Complete achlor-hydrria	0.45	6	0	11	Remains well 5 months
191	Uniform rise and fall	2.0	27	41	Complete achlor-hydrria	0	12	0	43	Pain after 5 months
234	Climbing type	2.45	58	64	Sharp rise. Plateau	2.45	8	74	80	Well on discharge
207	—	—	33	54	Low climbing type	2.45	12	46	58	Recurrent ulcer
163	—	—	—	—	Complete achlor-hydrria	2.0	12	0	31	Pain after 5 months
172	—	—	33	48	Complete achlor-hydrria	2.30	12	0	47	Pain after 3 years

III. *After Resection of Ulcer, with Posterior Gastro-jejunostomy alone.*

178	Uniform rise and fall	2.30	45	58	Complete achlor-hydrria	2.45	12	0	41	Remains well 2 months
39	Low hypochlor-hydrria	1.30	19	44	Almost complete achlor-hydrria	1.30	7	0	32	Occasional vomiting
100	Hypochlor-hydrria	1.15	21	37	Slight rise and fall	2.45	12	0	45	Remains well 9 weeks
188	—	—	52	70	Complete achlor-hydrria	0.15	12	0	20	Occasional vomiting
111	—	—	—	—	Delayed rise. Plateau	1.45	6	57	74	Pain after 7 months

IV. *After Simple Excision of Ulcer.*

101	—	—	25	40	Complete achlor-hydrria	1.45	1	0	13	Haematemesis after 3 months
267	—	—	38	51	Hypochlor-hydrria	2.15	6	21	37	Recurrent ulcer

on the anterior aspect of the first part of the duodenum. Before operation his test meal chart showed the typical finding for duodenal ulcer, though with some delay. Fourteen days after operation he showed the same typical curve, with the plateau, however, 10 per cent. lower, and with less delay in emptying. He remained well three months, and then had a return of epigastric pain two hours after food.

Group III. After gastro-jejunostomy. In this group are included forty cases (see Tables V, VI, VII, and VIII), and these can best be considered under the following headings :

1. Effect of operation on the rate of emptying of the meal.
2. Effect on the regurgitation of bile into the stomach.
3. Effect on the acidity values, and the relation of post-operative acidity to the subsequent health of the patient.

1. *Rate of emptying.* Of the four cases examined after partial gastrectomy (Pólya-Mayo method) the meal invariably left the stomach within forty-five minutes, whereas before operation it had remained for three hours or more.

The remaining thirty-six cases have been examined in separate groups according to whether or not the pylorus had been occluded. The following figures show that the findings in either case are practically identical :

A. *With occlusion of pylorus.* In 70 per cent. of cases the meal disappeared more rapidly than before operation, the average time of emptying being one hour fifteen minutes. In 30 per cent. of cases the rate of emptying was either unaltered or else reduced, so that starch was often detected in the stomach content at the end of three hours.

B. *Without occlusion of pylorus.* In 67 per cent. of cases the meal disappeared more rapidly than before operation, the average time of emptying being one hour thirty minutes. In 33 per cent. of cases the rate of emptying was either unaltered or else reduced, so that starch was often detected in the stomach content at the end of three hours.

2. *Regurgitation of bile.* The observations here are based on the number of test meal specimens showing bile to the naked eye. Chemical tests for bile and trypsin were considered unnecessary. In the typical test meal after gastro-jejunostomy, the specimens are somewhat difficult to withdraw. Mucus and blood rarely appear, but bile is usually so copious as to stain each specimen an intense golden-yellow colour. In some cases specimens of high acid content become a deep green colour on standing in contact with the air ; more rarely they are found to be of this colour when aspirated from the stomach.

Of forty cases only one showed less bile than before operation. It appeared in six specimens, whereas previously it had appeared in eight. Of the remaining thirty-nine cases all showed deep bile-staining of six or more specimens of the twelve, and 75 per cent. showed bile-staining of ten or twelve specimens. Further, in this series bile was found in the fasting gastric fluid in twenty-six cases (or 90 per cent.). Of those four cases where it did not appear, in two the pylorus had been occluded, and in the other two it had not. The test meals had been performed from eleven days to seven years after operation. A grouped analysis of

the figures shows that occlusion of the pylorus makes no difference to the number of specimens containing bile.

3. *Post-operative acidity.* Speaking generally of this series it may be said that complete achlorhydria results from gastro-jejunostomy in about 50 per cent. of cases (see Fig. 9). Statistically, of course, the figures are useless, for, whereas many patients included here have been those applying for relief of symptoms following operation, many others who are well have not so applied.

Three months after Posterior Gastro-jejunostomy
for Duodenal Ulcer.

Case 73a. ♂ 27. 16 July 1921.

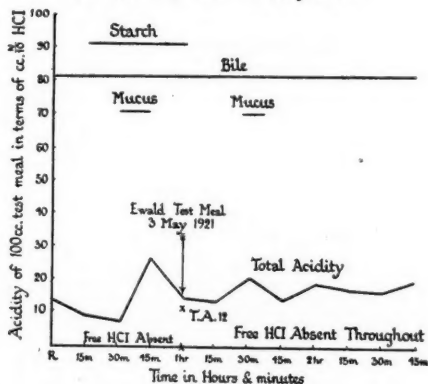


FIG. 9.

Description.—Specimens withdrawn with difficulty, especially towards the end. Small clean deposits up to 1 hour. Supernatant fluid bile-stained. Occasionally a little dirty mucus

Two weeks after operation, viz:—
Wedge Reaction of Ulcer of Body of Stomach;
Posterior Gastro-jejunostomy; and Occlusion of
Pylorus.

Case 234. ♂ 50. 2 March 1922.

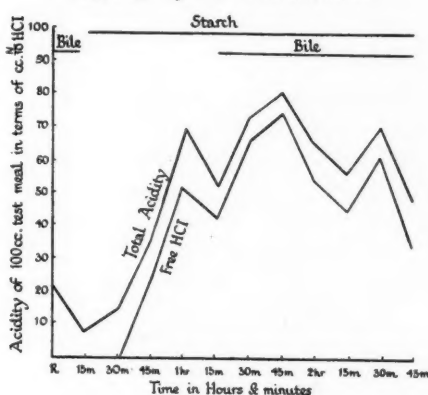


FIG. 10.

Description.—All specimens withdrawn with ease. Resting fluid turbid and copious, with very slight deposit only. Porridge visible to 2 hours. Supernatant fluid turbid.

Where complete achlorhydria does not supervene (see Fig. 10), the type of curve usually conforms closely to that found before operation, though the maximum points may be somewhat higher or lower. Thus, after operation for duodenal ulcer, the plateau may persist though placed at a somewhat higher or lower level. Similarly, the effect after operation for pyloric ulcer may be that a curve of the high climbing type becomes one of the low climbing type. In only a small proportion of cases does a curve of high acidity give place to one of low hypochlorhydria; the rule being, either that complete achlorhydria supervenes, or else that the original curve of high acidity persists.

In comparing acidity before and after operation the actual configuration of the curve seems of little significance, and only the maximum point attained by the free HCl curve need be considered. Reference to Table VIII will show the forty cases under consideration, grouped in three columns according to whether—(1) the free HCl was abolished; (2) the maximum free HCl point, though depressed, remained high; or (3) the maximum free HCl point became higher.

The cases in Table VIII are placed in two groups, according to whether or not the pylorus was occluded. Where it was not occluded the free HCl was abolished in ten cases out of nineteen; where it was occluded a smaller proportion showed absence of free HCl, namely, eight cases out of twenty-one.

Concerning the subsequent health of the patients the records of the 'Follow Through' departments have been quoted (see Tables V, VI, VII, and VIII). Since, however, the series covers a period of less than two years these records are at present of limited value.

TABLE VIII. *Cases examined after Operation.*Group III. *Gastro-jejunostomy.*A. *Without Occlusion of Pylorus. 19 Cases.*

Acidity.	Free HCl abolished. 10 cases.		Remained high. 5 cases.	Became higher. 4 cases.
Duodenal ulcer	Remains well, 1. 3 months, 1	Pain after	Remains well, 1. Pain after 1 month, 1	Remains well, 1. Pain after 12 months, 2
Pyloric ulcer	Remains well, 1		Remains well, 1	Gastro-jejunal ulcer, 1
Ulcer of body of stomach	Remaining well, 4. Vomiting, 2. Pain since operation, 1		Pain after 3 years, 1. Pain after 7 months, 1	Nil

B. *With Occlusion of Pylorus. 21 Cases.*

Acidity.	Free HCl abolished. 8 cases.		Remained high. 8 cases.	Became higher. 5 cases.
Duodenal ulcer	Recurrent ulcer, 1		Remaining well, 3	Remains well, 1
Pyloric ulcer	Remaining well, 2. and discomfort, 1	Nausea	Remaining well, 4. Gastro- jejunal ulcer, 1	Remaining well, 2
Ulcer of body of stomach	Remains well, 1. 5 months, 2. years, 1	Pain after Pain after 3	Nil	Remains well, 1. Recurrent ulcer, 1

1. *Where free HCl was abolished.* It will be seen that where free HCl was abolished nine of the patients (50 per cent.) remained perfectly well. Of the other nine, two complained of vomiting, one of nausea and discomfort, and five of a recurrence of pain within three months to three years after operation. The remaining patient must be considered under the following heading:

Case 232. Ulcer of pyloric end of stomach after gastro-jejunostomy for duodenal ulcer. This was a man of 38, who complained of pain and recurrent haematemesis. Two years before the Ewald meal had shown free HCl 49 (0.18 per cent.) and total acidity 70, and gastro-jejunostomy with occlusion of the pylorus had been performed for duodenal ulcer. The test meal chart now showed complete achlorhydria with regurgitation of bile in all twelve specimens, but with marked delay in emptying. The abdomen was opened again, and the efferent jejunal loop was found bound down by adhesions. The obstruction was relieved by entero-anastomosis, but the patient ultimately died of acute intestinal obstruction; and, at autopsy, a healing, shallow, sub-acute ulcer (2 by 0.7 cm.) was found saddling the lesser curve, in the commencement of the pyloric canal.

2. *Where free HCl remained high or became higher.* Reference again to Table VIII will show that, in these groups, fourteen of the patients (64 per cent.)

remained perfectly well. Of the other eight, five complained of a recurrence of pain within one month to three years after the operation, two had gastro-jejunal ulcers, and one had a recurrent ulcer in the posterior suture line of a wedge resection. The three cases last mentioned will be briefly considered.

Case 105. Gastro-jejunal ulcer. This was a man of 42 years of age, who had been operated upon eight months before by posterior gastro-jejunostomy for a large pyloric ulcer. The Ewald meal before operation had been free HCl 38 (0.14 per cent.) and total acidity 57. After operation he was perfectly well for six months, and then began to complain of pain radiating from the umbilicus to the left iliac fossa, worse at night, and not definitely related to meals. The fractional test meal chart, eight months after operation, is reproduced in Fig. 11. The specimens were withdrawn with difficulty and were uniformly bile-stained, some turning deep green on exposure to the air. Starch was absent after one hour fifteen minutes. The resting fluid showed achlorhydria; the curve abruptly

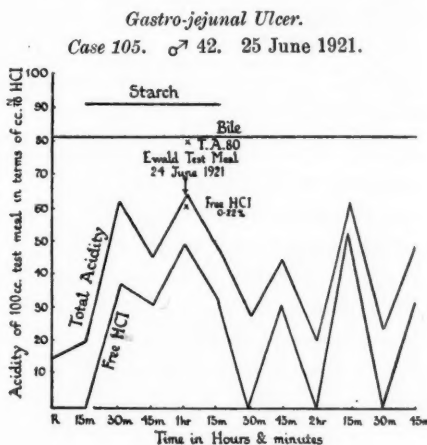


FIG. 11.

Description.—Specimens withdrawn with some difficulty. Uniformly bile-stained and deep green on standing. Scanty dirty deposits. No mucus.

rose to a peak at the one-hour point, where there was free HCl 48 (0.18 per cent.) and total acidity 64. Subsequently there were several sharp peaks, but the curve had a general trend downwards. A similar configuration is found in many post-operative cases, especially those where the anastomosis is of some years' standing. The depressions following the peaks probably indicate that the tube has slipped through the anastomosis, for they may occur when the tube is allowed to pass by accident into the duodenum in any pre-operative case where hyperacidity exists. A second laparotomy, twelve months after the first, revealed a large indurated ulcer involving the stoma and the afferent jejunal loop, and adherent to the transverse colon. The ulcer was excised and the stoma reconstructed. Fourteen days after this operation the fractional test meal was almost identical with the previous finding, though the maximum points were a little lower, namely free HCl 43 (0.16 per cent.) and total acidity 60.

Case 250. Gastro-jejunal ulcer. This was a man of 26, upon whom, two years before, had been performed gastro-jejunostomy with closure of a chronic pyloric ulcer for acute perforation. He subsequently had occurrence of pain late after food, coming on in attacks with definite free intervals. The fractional test

meal showed bile throughout, emptying rate two hours, and a curve almost identical with Fig. 10, where the maximum points were free HCl 49 (0.18 per cent.) and total acidity 59. At operation a shallow, non-indurated ulcer (1 cm. diameter) was found on the anastomosis, together with an erosion of the jejunal mucosa (0.5 cm. diameter) in the efferent loop, 3 cm. below the stoma.

Case 207. Recurrent ulcer of body of stomach. This was a woman of 49, upon whom, three years before, had been performed wedge resection of an ulcer of the body of stomach, posterior transverse gastro-jejunosomy, and occlusion of the pylorus. The Ewald meal before operation had been free HCl 34 (0.12 per cent.) and total acidity 54. Following the operation she was never really well, and, on readmission to hospital, had had continuous pain for twelve months, with frequent vomiting and with severe haematemesis two months before. The blood-count showed red blood corpuscles 3,420,000 per c.mm., and haemoglobin 65 per. cent. The fractional test meal showed bile-staining throughout, with marked delay in emptying. The resting fluid showed free HCl 34 (0.12 per cent.) and total acidity 50; the curve was of the climbing type, showing, at the maximum points, free HCl 46 (0.17 per cent.) and total acidity 58. At operation was found a large chronic ulcer in the posterior suture line of the previous wedge resection. It was 1.5 cm. across, had a very thickened edge, extended from the lesser curve to the upper aspect of the stoma, and was firmly adherent to the pancreas and mesocolon.

In the whole series the relation of post-operative acidity to the recurrence of ulceration may be summed up as follows:

In each of two cases of gastro-jejunal ulcer the post-operative acidity was high, viz. free HCl 48 (0.18 per cent.). A record of the acidity before operation is only available in one of these, where the maximum point for free HCl shows an increase, after gastro-jejunosomy, of 27 per cent.

Of ulcers occurring in the stomach after gastro-jejunosomy, in one case the acidity was higher after operation, free HCl being raised to 46 (0.17 per cent.), or an increase of 40 per cent. In the second case there was complete achlorhydria coexisting with secondary anaemia, the free HCl value having been reduced from 59 (0.22 per cent.) to nothing.

Finally, in a case where excision of ulcer had been performed without gastro-jejunosomy, a recurrent ulcer appeared, where the test meal showed 44 per cent. reduction of the previous finding for free HCl.

Hence, though high gastric acidity was a constant association of gastro-jejunal ulcer, recurrent ulcer occurred in the stomach when the free HCl was reduced below the limits of the normal or even abolished.

7. Carcinoma of the Stomach.

Of fifteen cases recorded in this group, ten are characterized by complete achlorhydria (see Table IX). Of the remaining five cases, two would pass for normal, two are of the climbing type, and one shows a sudden rise and a high plateau.

The cases may be divided into three groups: (1) Carcinoma without pyloric obstruction. (2) Carcinoma with pyloric obstruction. (3) Carcinoma arising in chronic gastric ulcer.

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Group I. Carcinoma without pyloric obstruction. In most cases of this group there was a large ulcerated carcinomatous mass astride the lesser curve, usually quite inoperable. In the five cases recorded, the specimens were usually difficult to obtain, were dirty, and contained mucus. In three cases large amounts of macroscopic blood appeared (see Fig. 12). The rate of emptying

TABLE IX. *Carcinoma of Stomach. 15 Cases.*

Case No.	Description of Specimens.	Bile.	Blood.	Mucus.	Type of Curve.	Time of Emptying.	Resting Fluid.		Maximum.		Ewald.	
							Free HCl.	Total Acidity.	Free HCl.	Total Acidity.	Free HCl.	Total Acidity.
4	Profuse black insoluble material	—	—	—	Complete achlorhydria	2.45	0	13	0	15	—	—
129	Dirty blood-stained turbid fluid	0	11	5	Uniform rise and fall	2.0	0	34	24	60	—	—
153	Dirty blood and mucus	0	11	2	Complete achlorhydria	0.30	0	13	0	21	0	7
224	Little deposit. Transparent fluid	7	0	2	Complete achlorhydria	1.0	0	13	0	13	0	30
235	Scanty turbid fluid. Dirty deposits	1	3	0	Complete achlorhydria	1.30	0	6	0	28	0	36
133	Specimens copious. Large deposits	1	0	0	Complete achlorhydria	2.45	0	19	0	28	0	10
244	Dirty curdled deposits	1	0	0	Complete achlorhydria	2.45	0	16	0	30	0	8
148	Copious turbid fluid. Large deposits	0	1	1	Low hypochlorhydria	2.45	0	29	18	40	0	24
57	Copious turbid fluid. Large deposits	0	0	0	Complete achlorhydria	2.45	0	51	0	54	—	—
154	Large offensive deposits	0	0	0	Complete achlorhydria	2.45	0	110	0	110	0	29
215	Copious cloudy fluid. Dirty deposits.	9	0	0	Low hypochlorhydria	2.30	0	11	33	45	20	44
180	Copious cloudy fluid. Dirty deposits	1	0	6	Uniform rise and fall	2.15	0	53	0	53	32	57
17	—	0	0	0	Climbing type	2.30	54	70	54	70	41	65
18	Dirty offensive fluid. Much deposit	0	0	0	Climbing type	2.45	45	78	14	109	26	48
88	Copious cloudy fluid. Large deposits.	2	0	0	Sharp rise. Marked plateau	2.45	18	46	46	86	33	49

was rapid, the average being one hour thirty minutes. In four cases there was complete achlorhydria, with a total acidity remaining below 20 throughout the test. However, one case differs markedly from the other four.

Case 17. This was a woman of 60, giving seven years' history of long attacks of epigastric pain with intervals in which freedom from symptoms was still perfect. The test meal showed no bile, and no delay in emptying. The

acidity of the resting fluid was free HCl 54 (0.20 per cent.) and total acidity 70. The curve was of the climbing type, and at the end of three hours it reached a point just short of that reached by the resting fluid. At operation a carcinomatous ulcer was found high up on the lesser curve, and this was confirmed histologically.

Group II. Carcinoma with pyloric obstruction. The usual finding in this group was carcinoma encircling the pyloric canal, and of eight cases four were inoperable. In appearance there is a remarkable constancy of the test meal findings. All the specimens show copious, dirty, curdled porridge deposits, which may completely fill every tube during the whole three hours. Correspondingly, of course, in every case starch is detected throughout, but in only one case was it found in the fasting gastric fluid. In no case was macroscopic

Carcinoma of Stomach.—Group I.

Case 153. ♂ 51. 21 September 1921.

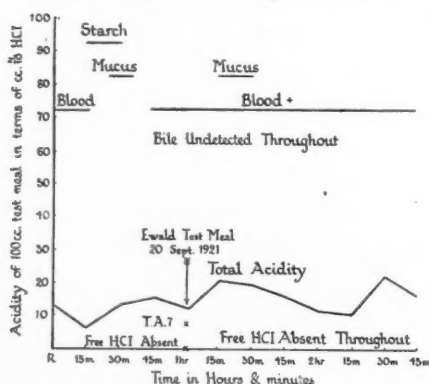


FIG. 12.

Description.—Specimens withdrawn with ease. All dirty and turbid, and majority stained bright red with blood. Porridge visible up to 30 minutes. Floating blood-stained mucus in most specimens.

blood found, and both bile and mucus rarely appeared. In six cases complete achlorhydria was found (see Fig. 13); but with the distinction from the previous group that the total acidity was much higher, and was found sometimes throughout the three hours to run at a level of 40, or even 60.

In this group two cases differ markedly from the other six.

Case 18. This was a woman of 47 years of age. She had a history of three months' epigastric pain late after food and recently continuous between meals, with vomiting, becoming of large amount, and loss of weight. The test meal showed offensive fluid, delayed emptying, and the climbing type of curve, attaining a maximum of free HCl 50 (0.18 per cent.) and total acidity 65 at the end of three hours. At operation the stomach was found hypertrophied, with an ulcerating carcinomatous mass obstructing the pylorus.

Case 88. This was a man of 49 years of age, with a history of twelve months' discomfort late after food, recently troubling him only at night. There

Carcinoma of Stomach.—Group II.

Case 57. ♀ 61. 24 January 1921.

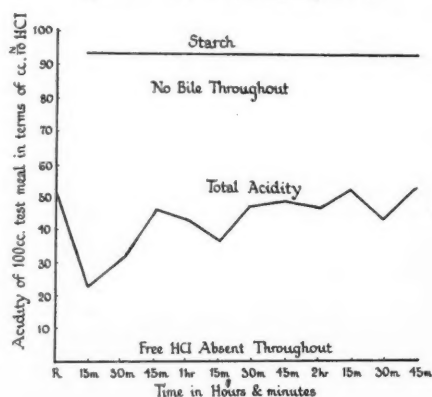


FIG. 13.

Description.—Specimens withdrawn with great ease. Large, dirty, curdled deposits. Supernatant fluid turbid. No blood. No mucus.

was a nodular epigastric tumour adherent to the liver. The test meal was of the type shown in Fig. 3, with dirty deposits and delayed emptying, the curve showing a high resting fluid, abrupt rise, plateau, and that wide separation between the two curves which indicates stasis or obstruction. The maximum free HCl was 58 (0.21 per cent.) and total acidity 86. At operation there was found infiltration by medullary carcinoma of the pyloric antrum, with direct spread into the liver. Partial gastrectomy was successfully performed, with removal of a portion of the liver. However, six months later, the patient died with carcinomatosis of the peritoneum and pleura.

Carcinoma arising in Chronic Ulcer of Body of Stomach.—Group III.

Case 180. ♀ 44. 28 October 1921.

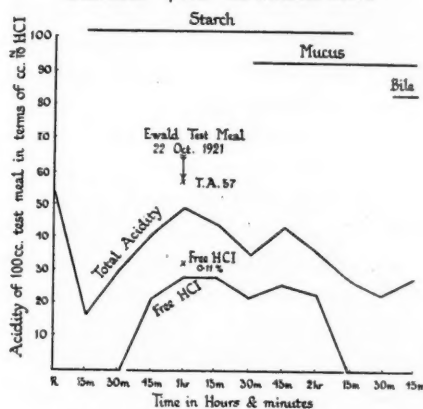


FIG. 14.

Description.—Specimens withdrawn with ease. Resting fluid and all subsequent specimens dirty and discoloured. Dirty deposits visible throughout; supernatant fluid turbid.

Group III. Carcinoma arising in chronic gastric ulcer. Two analogous cases fall into this group, and only one need be described here.

Case 180. This was a woman of 44 years of age, with a past history of chronic ulcer, in which the attacks had become longer and the intervals shorter, with, recently, pain continuous between meals but worse half an hour after food, and vomiting. The test meal (see Fig. 14) showed a dirty resting fluid, and discoloured specimens, with turbid supernatant fluid and dirty deposits. Blood was absent. There was little bile, but much mucus, and emptying occurred at two hours fifteen minutes. The curve showed achlorhydria in the resting fluid, and then a uniform rise and fall, the maximum points being free HCl 28 (0.10 per cent.) and total acidity 49. At operation was found a hard, irregular mass on the posterior surface of the body of the stomach, adherent to the pancreas, with secondary growth in the glands and nodules in the peritoneum. Successful partial gastrectomy was performed. Histologically the mass showed 'solid and tubular, spheroidal and polygonal-celled carcinoma arising in chronic progressive peptic ulcer of body of stomach', with similar growth in the lymphatic glands of the greater and lesser curves, and in a gland from the peritoneum.

The findings in these two cases show maximum points only 30 per cent. lower than the average figure for the corresponding non-malignant ulcer. This corroborates the current teaching (5), that where malignant changes supervene in chronic gastric ulcer, the acidity may remain above the limits of the normal.

In all the cases of carcinoma of the stomach the readings for the Ewald meal, taken at one hour, closely correspond with the maximum fractional readings.

8. *Visceroptosis.*

Of the seven cases occurring here, four were in women and three in men, all from 40 to 50 years of age (see Table IV). Certain departures from the clinical history and findings of visceroptosis had raised the question of gastric ulcer in three cases, of carcinoma of the stomach in two cases, of hour-glass stomach in one case, and of gall-stones in one case. At operation none of these conditions was found, but there were varying degrees of gastropstosis and general visceroptosis, with mobile colon and kidneys, and sometimes with a mesocolic fold, Jackson's membrane, and Lane's kink.

In five cases the test meal findings are identical. The specimens are withdrawn only with difficulty, and the resting fluid is dirty and opalescent, with a greyish mucoid deposit, though actual mucus is rarely present. Very little bile regurgitates, and starch may disappear in thirty minutes, the average rate of emptying being one hour. There is complete achlorhydria, often with the curve of total acidity extremely low, perhaps running along the line 6 or 10.

Two cases are totally unlike the five described above. Each was explored on suspicion of gastric ulcer, and it is with some reluctance that I mention them in this series, since a negative finding in exploratory laparotomy is no absolute proof of the absence of gastric ulcer.

Case 174. This was a woman of 37 with a history of ten years' vague attacks of discomfort after food, becoming more definite and showing periodicity in the past two years. The test meal shows delayed emptying, slight regurgitation of bile, and a curve with uniform rise and fall, the maximum points being free HCl 34 (0.12 per cent.) and total acidity 47. At operation marked gastropstosis and mobile colon were found.

Case 61. This was a man of 50 who gave a vague history of pain after food, in short attacks, for twenty years. Recently he had been troubled also by large foul vomits. His test meal was of the climbing type, with a wide interval between the curves, and a high-resting fluid. The maximum points were free HCl 31 (0.11 per cent.) and total acidity 59. There was marked delay in emptying, with copious thick, brown deposit in all the specimens. At operation the stomach was found dilated and prolapsed, and the dilatation extended into the duodenum. No ulcer nor scar was found.

In all the cases of visceroptosis the readings for the Ewald meal, taken at one hour, exactly correspond with the maximum fractional readings.

9. *Chronic Appendicitis.*

Except in one case of typical relapsing appendicitis a correct diagnosis was rarely made before operation in cases of this group. The patients all had a long history of abdominal symptoms atypical of any definite condition. After full inves-

FRACTIONAL TEST MEAL IN GASTRO-INTESTINAL DISORDERS 123

tigation, laparotomy was advised on the suspicion of chronic appendicitis in three cases, of chronic gastric ulcer in two cases, of gall-stones in one case, of visceroptosis in one case, and in one to determine the causation of severe recurrent haematemesis. At operation none of these conditions was found, but the appendix invariably showed submucous fibrosis and muscular hypertrophy, sometimes with concretions, fibrous constrictions, and peritoneal adhesions.

TABLE X. *Chronic Appendicitis. 9 Cases.*

Case No.	Withdrawal.	Description of Specimens.	Bile.	Blood.	Mucus.	Type of Curve.	Time of Emptying.	Resting fluid.		Maximum.		Ewald.	
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.	Free HCl.	Total Acidity.
233	Fair ease	Small deposits. Turbid fluid	0	0	2	Uniform rise and fall	2.0	0	6	44	51	—	—
139	Ease	Small deposits. Clean fluid	2	0	5	Uniform rise and fall	2.0	0	29	16	34	36	53
24	—	—	2	0	0	Uniform rise and fall	1.45	0	11	24	42	0	20
75	—	—	1	0	1	Uniform rise and fall	2.0	22	35	36	52	47	66
165	Fair ease	Small deposits. Clean fluid	4	0	2	Uniform rise and fall	1.45	0	12	31	45	—	—
96	Ease	No deposits. Opalescent fluid	0	0	0	Uniform rise and fall	0	0	7	25	36	55	73
64	—	—	7	0	0	Complete achlorhydria	2.0	0	22	0	22	—	—
36	—	—	4	0	0	Climbing type. Falls off	2.30	55	68	55	68	54	83
86	Ease	Clean deposits. Transparent fluid	0	0	0	Very sharp rise. Plateau	2.15	19	32	109	118	33	56

Of nine cases in this group six show identical findings (see Table X). The specimens are fairly easily obtained, showing opalescent or slightly turbid fluid with clear deposits (see Fig. 15). Mucus commonly appears, but bile is only occasionally found. The average rate of emptying is two hours, and is very constant. There is achlorhydria of the resting fluid, and the curve shows a uniform rise and fall, with the maximum points occurring at one hour thirty minutes, the average being free HCl 29 (0.10 per cent.) and total acidity 43.

Of the remaining three cases, two show hyperchlorhydria and one shows achlorhydria.

Case 86. This was a man of 56 with a history of two years' flatulence and discomfort. Recently he had had pain in the left upper abdomen, unrelated to food. The test meal was remarkable in showing a very copious secretion of transparent fluid, with little deposit. Emptying occurred in two hours fifteen minutes. The resting fluid showed achlorhydria, and the curve was of the high plateau type, with an abrupt rise to a maximum of free HCl 109 (0.40 per

cent.) and total acidity 118. At operation the appendix was bound down by adhesions, and the stomach and duodenum were normal. Eleven days after operation the test meal finding was identical.

Case 36. This was a woman of 23 with a history of attacks of epigastric pain lasting two days at a time. She had recently had continuous symptoms for three months, and the pain had become definitely related to food. The test meal was of the climbing type, with a wide interval between the curves. Emptying was delayed to two hours thirty minutes. The resting fluid showed free HCl 55 (0.20 per cent.) and total acidity 68, the curve climbing to a similar level at the two-hour point. No post-operative observations were made.

Chronic Appendicitis.

Case 165. ♀ 39. 14 October 1921.

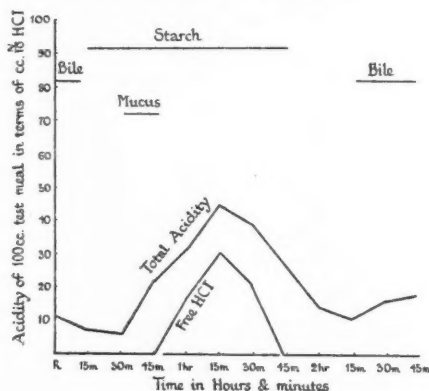


FIG. 15.

Description.—Specimens withdrawn with difficulty. Clean deposits; translucent supernatant fluid, with scattered clean mucoid flecks.

Case 64. This was a boy of 12 who was first treated for vomiting bright red blood in large amounts on four consecutive days. On this occasion the blood-count showed 2,050,000 red cells per cubic millimetre, and 35 per cent. haemoglobin. He made a gradual recovery, and four weeks later the red cells were 4,180,000 per cubic millimetre, and the haemoglobin 55 per cent. At this time the test meal showed complete achlorhydria, with total acidity less than 20, and emptying in two hours. He remained well for eight months, when severe haematemesis recurred. At operation there was no sign of chronic gastric ulcer, the haematemesis doubtless being due to multiple acute erosions of the gastric mucosa. The appendix showed submucous fibrosis and muscular hypertrophy with constrictions, films showed pus, and sections showed cellular infiltration of the muscular and peritoneal coats. On discharge from hospital the Ewald test meal showed complete achlorhydria, but the blood-count was not recorded.

In all the cases of chronic appendicitis the correspondence with the Ewald test meal is very poor. It usually shows a reading higher than the maximum fractional findings, often by as much as 20 per cent.

10. *Diseases of the Gall-bladder, Bile Passages, and Pancreas.*

In this group sixteen cases were investigated, chiefly from the point of view of differential diagnosis (see Table XI). They will be considered briefly under the following headings :

(1) *Gall-stones with acute cholecystitis.* Of the two cases recorded the findings are similar. The specimens are clean and fairly easily obtained. A little bile regurgitates, and emptying is delayed. The curves show a uniform rise and fall, with a maximum at the two-hour point, where the free HCl is 43 (0.16 per cent.) and total acidity 54. In one of the cases the fasting fluid shows free HCl 48 (0.18 per cent.) and total acidity 55 ; in the other it shows achlorhydria.

(2) *Gall-stones with chronic cholecystitis.* Of the four cases recorded here the results are practically identical, and are very similar to those of acute cholecystitis. The specimens are obtained with difficulty, and are clean. Bile usually regurgitates, and emptying may occur in two hours, but is often delayed. The curves show achlorhydria in the resting fluid, and an abrupt rise and fall. The maximum point occurs at about one hour thirty minutes, with free HCl 43 (0.16 per cent.) and total acidity 59.

These results are not in accordance with the current teaching (5), that in gall-stones low gastric acidity is the rule, and absence of free HCl common.

(3) *Chronic cholecystitis.* One case is recorded where no gall-stones were found, but sections of the gall-bladder showed slight chronic inflammation. Here there were clean, fairly copious specimens showing complete achlorhydria, with total acidity varying between lines 10 and 24. Emptying occurred in two hours fifteen minutes.

(4) *Cases with obstruction of the common bile-duct.* Of eight cases recorded in this group obstruction of the common bile-duct was due in three cases to carcinoma of the head of the pancreas, in one case to carcinoma of the ampulla of Vater, in one case to carcinoma of the gall-bladder, in two cases to impacted calculi, and in the last case to a stricture of undetermined origin.

The test meal findings are not identical, but they agree in the fact that the maximum points are all remarkably high, the average being free HCl 65 (0.24 per cent.) and total acidity 78. Four of the cases (see Fig. 16) show copious transparent fluid, with a high acidity in the fasting stomach content, an abrupt rise, and a marked plateau. Emptying is usually delayed, but in all other respects the charts are identical with those of uncomplicated duodenal ulcer.

Among the remaining cases (see Fig. 17) one shows a very steep curve of the persistently climbing type, reaching a final level of free HCl 83 (0.30 per cent.) and total acidity 96. Here there is delayed emptying, and the specimens are copious, turbid, and easily obtained. The remaining three cases show curves climbing to a high level in the second hour, but falling off in the third hour.

It was not possible to determine accurately the degree of obstruction caused in each case ; but, if this be estimated by the nature of the lesion and the intensity of the jaundice, it is found that the highest acidity coincides with the greatest

TABLE XL. *Diseases of the Gall-bladder, Bile Passages, and Pancreas. 16 Cases.*

Case No.	With-drawal.	Description of Specimens.	Bile.	Blood.	Mucus.	Type of Curve.	Time of Emptying.	Resting Fluid.		Maximum.		Ewald.	
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.	Free HCl.	Total Acidity.
Gall-stones.	193	Ease Clean deposits. Opalescent fluid	2	0	0	Uniform rise and fall	2.30	48	55	48	55	36	62
	199	Fair ease Clean deposits. Turbid fluid	1	0	0	Uniform rise and fall	2.45	0	12	45	55	—	—
	205	Ease Clean deposits. Opalescent fluid	3	0	0	Uniform rise and fall	1.30	0	28	26	59	0	36
	146	Fair ease Clean deposits. Opalescent fluid	1	2	0	Inter-rupted rise and fall	2.15	0	20	53	70	—	—
	166	Fair ease Clean deposits. Turbid fluid	4	0	0	Complete achlor-hydrria	2.15	0	28	0	28	0	15
	189	Much difficulty Dirty deposits. Cloudy fluid	6	0	0	Uniform rise and fall	2.45	0	10	27	53	—	—
	170	Some difficulty Dirty deposits. Cloudy fluid	3	0	7	Uniform rise and fall	2.45	0	9	39	53	55	75
Obstruction of Common Bile-duct.	237	Ease Clean deposits. Opalescent fluid	2	0	3	Sharp rise. Plateau	2.45	70	78	70	78	—	—
	230	Diffi-culty Small deposits. Clear fluid	1	0	0	Sharp rise. Plateau	1.30	34	48	83	89	22	37
	258	Ease Clean deposits. Opalescent fluid	1	0	0	High climbing type	2.45	0	10	83	96	—	—
	222	Ease Clean deposits. Transpa-rent fluid	0	0	0	Slow rise. Plateau	2.45	0	16	48	59	63	72
	206	Ease Clean deposits. Translu-cent fluid	1	0	0	Sharp rise. High pla-teau	2.15	68	76	86	97	41	61
	84	Great ease Large deposits. Transpa-rent fluid	0	0	0	Sharp rise. Low pla-teau	2.45	0	22	44	60	41	61
	74	Fair ease Clean deposits. Transpa-rent fluid	0	0	0	Uniform rise and fall	2.0	19	39	52	68	17	40
	27	— —	1	0	0	Climbing type	2.15	36	57	33	71	14	29
	58	— —	0	0	2	Uniform rise and fall	2.15	0	25	54	73	—	—

obstruction. The recent work of Bolton and Goodhart (6) on duodenal regurgitation into the stomach explains the phenomenon of such very high curves; for, in the above cases, pancreatic secretion and bile are largely or completely cut off from the stomach, so that neutralization by their combined alkali contents fails, and therefore the terminal drop in the test meal curve does not occur.

In all cases of this group the readings for the Ewald meal, taken at one hour, correspond fairly well with the maximum fractional findings, except in some cases of gall-stones where the Ewald meal recorded achlorhydria, whereas, at some subsequent point, the fractional reading attained the level of normal acidity.

Carcinoma of Pancreas obstructing Common Bile-duct.

Case 206. ♂ 37. 27 November 1921.

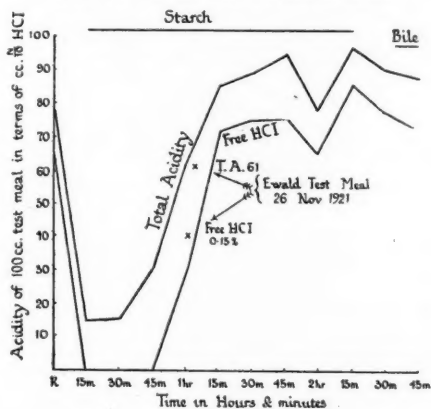


FIG. 16.

Description.—Specimens withdrawn with ease. Clean deposits; full volume of porridge up to 1 hour. Supernatant fluid translucent. No mucus.

Obstruction of Common Bile-duct (Cause undetermined).

Case 258. ♀ 40. 13 March 1922.

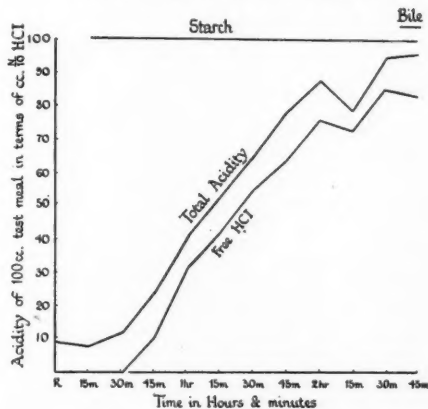


FIG. 17.

Description.—Specimens withdrawn with ease. Clean deposits; full volume of porridge up to 1 hour. Supernatant fluid clear. No mucus.

11. *Functional Disorders.*

Of eight cases recorded here, the diagnosis, prior to laparotomy, had been duodenal ulcer in three cases, and gastric ulcer, gall-stones, chronic appendicitis, carcinoma of stomach, and carcinoma of colon in the remainder. At operation, however, in no case was any pathological lesion discovered in the abdomen.

The cases fall into three classes according to the types of response to the test meal, namely:

(1) *Simple hyperchlorhydria.* In each of two cases belonging here duodenal ulcer had been diagnosed. One will be considered in detail.

Case 196. This was a man of 25 who had had three short attacks of pain, the first two lasting one week, the other four weeks. The total history was only eighteen months, and between the attacks he had been perfectly well. The pain was dull, strictly localized to the epigastrium, and occurred three hours after food. It was relieved by food and did not occur at night. The opaque meal showed

slight delay, with no deformity and no hyperperistalsis. The fractional test meal very strongly suggested duodenal ulcer, being identical with Fig. 1. At operation no abnormality was found in the abdomen. Nothing abnormal was seen on the duodenum nor felt through its walls. Finally, the duodenum was explored, but the mucous surface showed no erosion nor ulcer. Finney's pyloroplasty was performed.

(2) *Simple hypochlorhydria.* Three cases fall under this heading. All had indefinite abdominal symptoms. In one a normal gall-bladder was removed, and in one a normal appendix. The third was a man of 48 whose abdomen was opened to exclude carcinoma of the stomach.

In all three the test meal showed complete achlorhydria during the whole of three hours. The specimens were scanty, and emptying occurred in two hours. The average maximum total acidity figure was 34.

(3) *Normal acidity.* Of three cases occurring here one was suspicious of carcinoma of the colon, and the second had a doubtful history of gastric ulcer. The third will be considered in detail.

Case 182. This was a man of 39 with fourteen months' history of upper abdominal pain late after food. It occurred in short attacks of three or four days, and the periodicity was very imperfect. The opaque meal demonstrated a small hypertonic stomach, often showing four simultaneous peristaltic waves. There was hyperperistalsis of the duodenum with regurgitation through the second stage. The test meal chart showed scanty turbid specimens, with emptying rate two hours. The curve showed a slight uniform rise to a maximum of free HCl 37 (0.14 per cent.) and total acidity 48. At operation no abnormality was found.

Pylorospasm associated with Congenital Cystico-colic Band.

Case 273. ♂ 17. 23 June 1922.

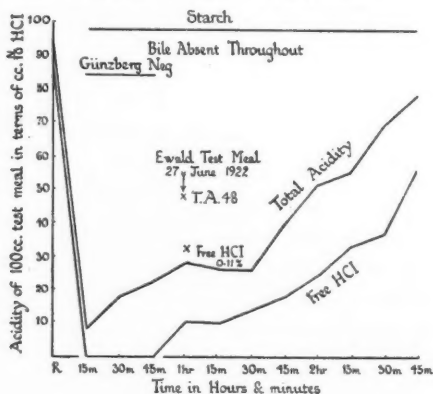


FIG. 18.

Description.—Specimens withdrawn with ease. Resting fluid, copious, opalescent—small clean mucoid deposit. Supernatant fluid colourless—deposits clean.

12. Peritoneal Bands and Adhesions.

Under this heading are two cases where some disturbance of motility of the stomach was associated with gross secretory abnormality.

Case 273. This was a boy of 17 with a history of epigastric pain and vomiting, recurring in short attacks of three or four days over a period of eleven years. The test meal chart (see Fig. 18) showed very copious, clear, resting fluid with free HCl 88 (0.33 per cent.) and total acidity 95. The curve was of the high climbing type, and the specimens showed clean deposits and colourless supernatant fluid. This is a typical picture of the effect on the gastric secretion of spasm of the pylorus. Opaque meal examination showed no abnormality other than slight gastropnoia. A diagnosis of appendicular gastralgia was made, and the abdomen explored through an upper right rectus incision. A normal appendix was removed. No abnormality was discovered in the stomach, duodenum, nor gall-bladder, but a broad congenital band was found passing across the first part of the duodenum from the fundus of the gall-bladder to the transverse mesocolon. This was divided between ligatures.

The symptoms in this case can be explained by recurrent pylorospasm, due to a disturbance of function of the pylorus owing to the presence of the band. Post-operative observations on the gastric function in this case have not yet been made.

Case 239. This was a man of 26 whose symptoms dated from five years before, when appendicectomy had been performed twenty-four hours after the onset of acute symptoms. The abdomen was not drained. He complained of attacks of pain with a definite periodicity, where the intervals were getting shorter. The pain commenced either late after food or else immediately after, first appearing in the epigastrium and then 'all over'. It was relieved by recumbency and by vomiting, which was self-induced. The opaque meal showed a hypertonic stomach, a defect in the duodenal cap, and hyperperistalsis of the duodenum. The test meal showed complete achlorhydria during the whole of three hours. The specimens were copious, and emptying occurred in one hour fifteen minutes. In spite of this a diagnosis of duodenal ulcer was made. At operation bands of inflammatory adhesions were found passing from the fundus of the gall-bladder to the second part of the duodenum. There was no abnormality in the stomach nor duodenum, but the pelvic viscera were involved in a mass of dense adhesions.

13. *Cirrhosis of Liver.*

In the five cases examined (three of hobnail cirrhosis and two of gummatous cirrhosis) the findings are practically identical (see Table XII). The specimens are withdrawn only with great difficulty, and it may be impossible at any time to obtain more than 5 c.c. The fasting fluid is usually scanty and turbid, with a dirty, grey deposit containing mucus. After porridge has disappeared, the specimens show a grey mucoid deposit with turbid supernatant fluid. Bile often regurgitates in large amounts, and is usually present in more than four specimens. A trace of blood may appear. Rapid emptying invariably occurs, the average time being one hour fifteen minutes. In all cases except one, complete achlorhydria is found, and here the condition is one of such low hypoachlorhydria that free HCl appears only in two specimens, the maximum points being free HCl 18 (0.07 per cent.) and total acidity 46. In all other cases the total acidity runs between the 10 line and the 20 line.

TABLE XII.

Cirrhosis of Liver. 5 Cases.

Case No.	Withdrawal.	Description of Specimens.	Bile.	Blood.	Mucus.	Type of Curve.	Time of Emptying.	Resting Fluid.		Maximum.		Ewald.	
								Free HCl.	Total Acidity.	Free HCl.	Total Acidity.	Free HCl.	Total Acidity.
83	Great difficulty	Scanty, turbid fluid	10	2	0	Complete achlorhydria	0.45	0	11	0	11	—	—
124	Great difficulty	Scanty, dirty, turbid fluid	1	0	0	Complete achlorhydria	1.0	0	13	0	22	0	28
130	Great difficulty	Very small dirty specimens	5	2	2	Complete achlorhydria	1.15	0	15	0	24	—	—
195	Some difficulty	Scanty, turbid fluid	6	0	0	Complete achlorhydria	1.30	0	6	0	12	29	49
126	Fair ease	Scanty, dirty, turbid fluid	2	1	1	Low hypochlorhydria	1.15	0	8	18	47	44	64

Pernicious Anaemia. 5 Cases.

55	Great difficulty	Scanty, turbid fluid	6	0	5	Complete achlorhydria	0.45	0	7	0	11	0	4
238	Some difficulty	Scanty, turbid fluid	2	0	3	Complete achlorhydria	0.45	0	4	0	8	0	8
78	Some difficulty	Dirty deposits. Turbid fluid	2	0	0	Complete achlorhydria	2.0	0	11	0	15	—	—
80	Great difficulty	Dirty deposits. Turbid fluid	3	0	5	Complete achlorhydria	1.15	0	6	0	9	—	—
236	Ease	Small deposits. Turbid fluid	0	0	0	Complete achlorhydria	2.0	0	11	0	14	—	—

Myeloid Leukaemia. 1 Case.

136	Fair ease	Copious fluid. Clean deposits	0	0	5	Low hypochlorhydria	2.30	0	9	14	40	0	31
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14. *Anaemias.*

It has already been shown that a secondary anaemia may result in achlorhydria (see p. 124), and that this may remain after recovery of the blood condition to normal (see p. 101).

Of the so-called primary anaemias, six cases have been examined (see Table XII), namely, five of pernicious anaemia and one of myeloid leukaemia. In all the cases of pernicious anaemia the findings were identical, namely, complete achlorhydria with hyposecretion and rapid emptying. The specimens were as described for cases of cirrhosis of the liver, though dirty tenacious mucus was more in evidence. The level of the total acidity reading is lower than in any

other group of cases, being always below the 12 line, and quite often running along the 6 line (see Fig. 19).

In the case of myeloid leukaemia the specimens were scanty but fairly easily obtained. The supernatant fluid was translucent, mucus appeared in three specimens, no bile regurgitated, and emptying occurred at two hours thirty minutes. Achlorhydria was almost complete, free HCl only appearing at one point where it registered 16 (0.06 per cent.) with a corresponding maximum total acidity of 40.

Pernicious Anaemia.

Case 55. ♀ 53. 22 January 1921.

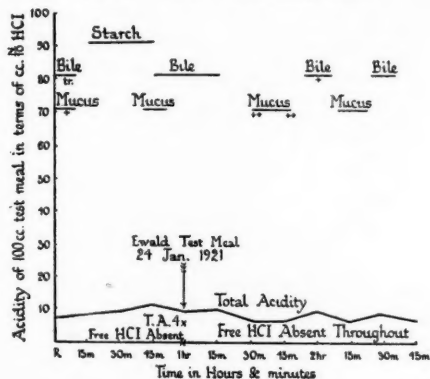


FIG. 19.

Description.—Specimens withdrawn with great difficulty: most of them being only 5 c.c. Much mucus. Porridge visible to 1 hour. Then dirty turbid fluid.

15. *Diseases of the Skin.*

It is not intended to make any deductions from cases of this group, since only three have been recorded. Two cases of acne rosacea showed pronounced hypochlorhydria, with scanty mucoid specimens, and a tendency to rapid emptying. A similar condition was present in 58 per cent. of cases of acne rosacea recently examined by Ryle and Barber (7). The third case was one of lupus erythematosus.

Case 81. This was a woman of 39, with lupus erythematosus of seven years' duration. She had suffered for eight years from attacks of pain immediately after food with occasional vomiting, and the onset of the skin eruption dated from a severe and prolonged attack of such symptoms. The test meal chart shows that the specimens were withdrawn with some difficulty, but little mucus appeared. Emptying occurred in one hour thirty minutes. The curve shows hypochlorhydria with free HCl appearing twice in the second hour. The reading here is free HCl 29 (0.10 per cent.) and total acidity 43.

16. *Carcinoma in Organs other than the Stomach.*

Four cases were examined with a view to determining whether carcinoma in organs other than the stomach had any influence on gastric secretion. Two cases were of carcinoma of the oesophagus, one of carcinoma of the rectum, and the last

of carcinoma of the lung. In the first three of these cases the curve of free HCl fell within the limits of normal. In the last case it rose at the one-hour point to a level 20 per cent. higher than the prescribed normal.

Summary.

In the course of an investigation extending over two years the fractional method of gastric analysis was applied to 270 patients. In 174 of these cases the diagnosis was considered proved. The remaining ninety-six cases were omitted, since in these the diagnosis remains unproved. The cases were grouped according to the anatomical findings at operation or autopsy.

1. Fifteen cases of chronic ulcer of the duodenum were investigated. The fractional test meal findings were found to be remarkably constant. 88 per cent. of cases showed curves considerably above the limits of normal. In every uncomplicated case there was copious secretion of transparent fluid and rapid emptying. The acidity was high in the fasting stomach content, and the curve showed an abrupt rise with a high plateau. Where the condition was complicated by stenosis emptying was delayed, and the curves showed a gradual climb to a high level.

2. Fifteen cases of chronic ulcer of the pyloric end of the stomach were investigated. Though the findings were less constant, 67 per cent. of cases showed curves above the limits of normal. The typical curve was one with a high resting fluid, a gradual climb to a high level, and a slight terminal drop. Emptying was delayed. Slight degrees of pyloric obstruction did not alter the configuration of the curve; but, where obstruction was considerable, great disparity appeared between the curves for free HCl and total acidity, and very large dirty deposits occurred.

3. Twenty cases of chronic ulcer of the body of the stomach were investigated. There was no constant finding. In 50 per cent. of cases the curve remained within the limits of normal, while in 35 per cent. it rose above these limits. Speaking very generally, two types of curve were found, namely, one showing a uniform rise followed by a complete drop to the base line, and the other showing a gradual persistent climb to a fairly high level. There is some evidence that the latter was associated with pylorospasm. The acidity of the fasting stomach content was low, and in 70 per cent. of cases it contained no free HCl. An observation of some importance is that in 38 per cent. of cases, where the ulcer was situated posteriorly, macroscopic blood appeared.

4. In cases of hour-glass constriction of the stomach, and in a small group of cases with ulcer on the anterior aspect of the body of the stomach, the findings were similar. There was complete achlorhydria with rapid emptying, but, in contradistinction to other cases with complete absence of free HCl, there was found an excess of opalescent fluid and little mucus. Where pyloric obstruction existed as a complication the findings were as in pyloric ulcer.

5. Forty-three cases were examined after gastro-jejunostomy. All showed deep bile-staining of more than half the specimens, and in 90 per cent. of cases

bile was found in the fasting gastric fluid. In 70 per cent. of cases the meal disappeared more rapidly than before operation, the average time of emptying being one hour fifteen minutes. The curve after operation either showed complete achlorhydria or else was found to conform closely to that obtained before operation. However, in 23 per cent. of cases the maximum points for free HCl were higher after operation than before. Gastro-jejunostomy abolished free HCl in 45 per cent. of the cases examined. Finally, it was found in parallel series of cases that the regurgitation of bile, the rate of emptying, and the post-operative acidity were precisely the same whether the pylorus had been occluded or not.

6. In the two cases of gastro-jejunal ulcer investigated the acid curves were above the limits of normal. Where recurrent ulceration occurred in the stomach the curves were below the normal limits in two cases, and in one case there was complete achlorhydria.

7. Fifteen cases of carcinoma of the stomach were investigated. In 67 per cent. the curves showed complete achlorhydria. The specimens were usually copious and contained dirty mucus. Macroscopic blood appeared in 27 per cent. of cases, of which half were operable. Unless the growth obstructed the pylorus there was rapid emptying. With pyloric obstruction there was usually achlorhydria, and a very high total acidity, with marked delay in emptying. In 33 per cent. of cases the curves were within or above the limits of normal, and this group includes certain cases where growth obstructed the pylorus, and all the cases where malignant changes had supervened in chronic gastric ulcer.

8. Nine cases of chronic appendicitis were investigated. In 78 per cent. of these the curves were within the limits of normal. Of the exceptions one showed extreme hyperchlorhydria, and the other had complete absence of free HCl following a severe haematemesis.

9. Seven cases of gall-stones were investigated, some associated with acute cholecystitis, and some with chronic cholecystitis. In 83 per cent. of cases the curves fell within the normal limits.

10. Eight cases were investigated where the common bile-duct was obstructed. Very high acid curves, either of the plateau type or of the climbing type, appeared in 88 per cent. of cases.

11. In a great variety of conditions there occurred a complete achlorhydria, and the specimens were scanty, difficult to withdraw, and mixed with mucus. Such findings were invariably associated with rapid emptying. In the majority of cases examined of visceroptosis, pernicious anaemia, and cirrhosis of the liver these findings were present. In cases of myeloid leukaemia, acne rosacea, and lupus erythematosus there was a low hypochlorhydria.

12. A prolonged secondary anaemia, such as may be produced by repeated small haemorrhages from a duodenal ulcer, may result in achlorhydria. Further, this may remain after recovery of the blood condition to normal.

I take this opportunity of thanking Dr. Charles Miller, Dr. A. W. M. Ellis, and Dr. G. Riddoch, not only for their invariable kindness in placing beds in the

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To Dr. H. A. Ash, who has estimated the acidity of the last 100 test meals, to the Sisters and nurses who have so willingly rendered assistance in preparing the test meals and in aspirating the specimens, and to the students who assisted in duplicating my case records, I wish to tender my gratitude and thanks.

Finally, I have to acknowledge the kindness of Dr. T. I. Bennett and Dr. J. A. Ryle in allowing me to reproduce their chart representing the limits of the secretion of free hydrochloric acid in 80 per cent. of healthy males.

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MUSCULAR EXERCISE, LACTIC ACID, AND THE SUPPLY AND UTILIZATION OF OXYGEN

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Introduction.

MODERN progress in knowledge of the behaviour of muscle started from the researches of Fletcher (11, 12, 13) on the respiration of muscular tissue, and has been guided since by that landmark in exact physiology, the investigation by Fletcher and Hopkins (14) of lactic acid in surviving muscle. Hence arose a long series of investigations by many workers on the heat-production, the gaseous exchange, and the lactic acid and glycogen content of muscle; these have been summarized elsewhere (21, 23, 24). The insight thus acquired of the intimate physical and chemical mechanisms of the living muscle exceeds that of any other cell or process. In muscle we have several independent but convergent lines of progress, chemical, physical, and mechanical, and it is possible already to see, often not too dimly, from one to the other. Our knowledge is not, of course, in any single direction complete: it seemed sufficient,

however, to warrant an attempt to press to their logical conclusion, in the case of man, the principles established in working on isolated muscles, while it was to be hoped that such an attempt would throw further light, and suggest further lines of attack, on the more academic problems of the pure physiology of muscle. Hitherto, apart from an occasional reference to lactic acid in connexion with respiration, dyspnoea, or fatigue, there has been little realization of the extraordinary vigour of the chemical processes which occur in muscle, or of the clearness of the principles which govern them. With the generous help of the Medical Research Council the attempt has been made, and the following is a summarized account of some aspects of it, which we believe perhaps may be pertinent to medicine. During the course of our work it has been a continual surprise and incentive to find how precisely the principles established in the case of isolated frog's muscle are verified in the case of muscular exercise in normal man: and we have been encouraged thereby to hope that perhaps these same principles may be found already to bear some tentative application to the case of muscular exercise in the abnormal, and (among other things) to the phenomena of breathlessness.

We have adopted throughout the standpoint reached in modern investigation of the isolated muscle, and have attempted to show, by experiment and deduction, how application may be made to normal man. We have avoided more than an occasional reference to the possible clinical aspects of the facts and principles discussed.

A. *The Function of Oxidation in the Body.*

Oxygen is used in the combustion of food-stuffs to supply the energy required for bodily processes. Even in a state of complete rest the living cell requires oxygen in order to maintain its dynamic state of molecular organization, of readiness and power to respond to a stimulus. It is well known that a nerve deprived of oxygen gradually fails to conduct an impulse, though the amount of oxygen used is exceedingly small (1). In muscle the resting rate of oxygen consumption is much larger, but it has long been known that, especially at relatively low temperatures, a muscle will maintain its excitability for considerable periods in the complete absence of oxygen. This was believed to be due to the supposed fact that oxygen is taken in and stored in the living protoplasm for use in later need ('intramolecular oxygen'). There is no truth in this belief. The most rigorous exclusion of oxygen, even the entire prohibition of oxidation by poisoning with cyanide (46), still leaves the muscle active for a considerable period. Moreover, the magnitude of the 'initial' heat production¹ in a muscle twitch (45), and its time-relations (15), are totally unaffected by the presence or absence of oxygen. *Oxygen is not used in the primary break-down processes of rest or activity, which proceed uninfluenced*

¹ i.e. the heat liberated in the phases of contraction and relaxation, as distinguished from recovery.

for a time by its complete absence: *it is used only in what, strictly speaking, may be called recovery processes.*

If a living, resting, isolated muscle be deprived of oxygen it survives for a while; if the process be not pushed too far, and oxygen be restored to the muscle before it is too late, it then proceeds to make good its previous deficit in oxygen intake by a rise above its earlier resting value. If an isolated muscle be stimulated in oxygen there is a prolonged rise in its oxygen consumption, lasting for some time after the stimulus: if the muscle be stimulated in a chamber free from oxygen, and then, later on, oxygen be admitted, the rate of oxygen consumption rises above normal, and the total oxygen used in a long survival period is the same as if oxygen had been present throughout. The same phenomena, within limits, can be demonstrated in man. It is not practicable to deprive a man, as a whole, of oxygen: the brain is too sensitive to oxygen want. It is practicable, however, to deprive the human muscle of oxygen, in the sense that it is possible for a healthy man to take muscular exercise requiring far more oxygen than can conceivably be supplied through the circulation during the exercise itself, and to establish a heavy 'oxygen debt': indeed, as the result of 24 secs. only of severe exercise in a powerful man, we have found a total oxygen intake during the following 30 minutes of about $8\frac{1}{2}$ litres in excess of the resting value: 24 secs. of exercise led to a delayed consumption of oxygen sufficient to keep the subject comfortable in bed for more than half an hour. In another experiment more prolonged violent effort led to an oxygen deficit of $13\frac{1}{2}$ litres. Were it not for the fact that the body is able thus to meet its liabilities for oxygen considerably *in arrears*, it would not be possible for man to make anything but the most moderate muscular effort. We will consider this more fully later. It is obvious, however, that we must regard the muscle as capable of 'going into debt' for oxygen, of *committing itself to future oxidations on the security of lactic acid liberated in activity.*

We must distinguish therefore between three different quantities—oxygen 'intake', oxygen 'consumption', and oxygen 'requirement'. The first two may differ slightly, in so far as oxygen may (a) be taken in, in excess of consumption, to saturate blood previously reduced; and (b) be used in excess of intake at the expense of blood previously saturated: the difference is small. The third, however, may differ widely from the others, to the extent that 'expenditure' may largely exceed 'income', so long as the 'security' remains adequate. In the body the 'security' reaches its limit at the lactic acid maximum, and any further expenditure must be made out of 'income' of oxygen through the lungs and circulation. The 'security' given, lactic acid then forces the body later to pay off its debt out of income, in oxidative recovery.

B. *The Rôle of Lactic Acid in the Muscle.*

Lactic acid holds a very special position in the economy of the muscle. Like gas in the internal combustion engine its oxidation provides the power

required to do external work: like the gas, also, it is intimately concerned in the mechanism by which the work is done. It appears to be derived from the glycogen stored within the muscle, either directly or through the intermediation of a hexose diphosphate. In activity, or in prolonged rest without oxygen, lactic acid appears in the muscle (14): in recovery it reverts to glycogen, a small portion only being oxidized (35) (36). If an isolated muscle be kept at rest in oxygen, no lactic acid appears; it finally becomes inexcitable, but does not show the phenomena of *rigor mortis*. If the muscle be deprived of oxygen at rest, or if it be stimulated, lactic acid accumulates within it and corresponding glycogen disappears (36). Deprivation of oxygen pushed to its limit means *rigor mortis* and a lactic acid maximum of about 0.5 per cent. to 0.65 per cent.: stimulation, pushed to its limit, means inexcitability and a 'stimulation maximum' of lactic acid of about 0.24 per cent. to 0.4 per cent. Continued lack of oxygen, in a muscle stimulated to a standstill, leads to further lactic acid production and death. The introduction of oxygen to a muscle fatigued by stimulation, or by prolonged lack of oxygen, leads to an oxygen consumption and a heat-production far above the normal resting values, to a disappearance of lactic acid, and to a restoration of the glycogen: the muscle regains its previous excitability, recovery has occurred, and a subsequent stimulus will release lactic acid again. Moreover, Meyerhof has shown: (a) that the excess oxygen² and the excess CO₂ are equal, that the recovery process therefore has a respiratory quotient of unity, and involves the oxidation only of carbohydrate (or lactic acid); (b) that the oxygen and the CO₂ correspond to the total carbohydrate lost by oxidation in the complete cycle; (c) that when lactic acid appears glycogen always disappears in exactly corresponding amount; (d) that when lactic acid disappears in recovery, glycogen always reappears in corresponding amount, *less a quantity which, calculated from the oxygen consumption, has been lost by oxidation*; (e) that only about one-fourth of the lactic acid removed in recovery is oxidized: three-fourths has reappeared as glycogen.

Moreover, Meyerhof has shown (37) that the same phenomena occur, in an exaggerated degree, in muscle which has been finely chopped. Here, in the absence of oxygen, there is a rapid production of lactic acid: in the presence of oxygen the production of lactic acid is less, there is still a recovery process: the lactic acid, however, which has failed to appear has *not* been oxidized, since the total oxygen absorbed is only about one-fifth of the quantity which would have been required to complete the oxidation of that amount.

It is probable, from the work of the Embden School (9), that a hexose diphosphate $[C_6H_{10}O_4(H_2PO_4)_2]$ is an intermediary between glycogen and lactic acid, that it may indeed be the immediate precursor of lactic acid, the 'lact-acidogen' whose explosive transformation into lactic acid, on stimulation of the muscle, initiates the contractile process. Embden showed that, in muscle extract, glucose cannot be broken down into lactic acid, while hexose diphos-

² 'Excess oxygen' and 'excess CO₂' are used throughout this paper to express the amount of gas used, or produced, in excess of the resting value, in any given time.

phate can. Moreover, Meyerhof (37) has shown that only in the presence of phosphate can minced muscle transform all its preformed glycogen into lactic acid. Apart from these observations, the chemistry of the break-down and restoration of glycogen in the muscle remains at present a mystery. That phosphoric acid, however, has some special rôle in the process is shown by Embden's work, and it is of unusual interest that Embden, Grafe, and Schmitz (10) found the maximum muscular output of trained men to be considerably increased by the ingestion of phosphates.

C. *Heat-production.*

The contraction of a muscle has long been known to be accompanied by a production of heat: this heat appears more or less simultaneously with the mechanical response. Recent experiments, however, by A. V. Hill (20) and by Hartree and Hill (17) have shown that there is a further extensive production of heat, long delayed after the stimulus which caused it. In an isolated muscle stimulated in oxygen there is a prolonged evolution of heat, lasting for several minutes, which all evidence tends to connect with the oxidative removal of lactic acid in recovery (see Section N below). This recovery heat-production has told us much about the time-relations and other characteristics of the restoration process, following muscular activity. Other experiments by A. V. Hill (19), by Peters (40), and by Meyerhof (38), have shown that the total heat liberated in the anaerobic production of 1 gram. of lactic acid in muscle is about 370 calories. In its later oxidative removal (17) there is a further liberation of about 340 calories. In the complete cycle, therefore, in which 1 gram. of lactic acid is liberated and removed, and the muscle finally restored to its original state, there is a total evolution of 710 calories. But the heat of oxidation of 1 gram. of lactic acid is about 3,788 calories. Hence only a small fraction of the lactic acid can have been oxidized in recovery: in a muscle lightly stimulated, and with an adequate supply of oxygen, only about one molecule in five or six of the lactic acid is oxidized, the remainder being restored as glycogen during the recovery process.

Further experiments by Hartree and Hill (15) have shown that, in addition to this recovery process, there is an evolution of heat—(a) during the onset, (b) during the maintenance, of a contraction, and (c) during relaxation, and the analysis of these has led to the following picture of the mechanism involved. The muscle is to be regarded as an accumulator of energy, energy available for rapid non-oxidative discharge, stored during previous oxidations. In this respect it is similar to an electrical accumulator. The transformation of glycogen into lactic acid, the action of the lactic acid on the muscle proteins, and the neutralization of the lactic acid by the alkaline buffers of the muscle, are the vehicle by which this stored energy is made manifest: during recovery the process is reversed at the expense of a portion of lactic acid oxidized. The accumulator has been recharged, at the expense of oxidations required to run the dynamo.

We must regard the muscle therefore as possessing two mechanisms: (a) the anaerobic one of discharge, and (b) the oxidative one of recovery. These two mechanisms are probably distinct from one another; the first may certainly act without the second, the second without the first, and their efficiencies may vary independently. The speed, vigour, and efficiency of contraction and the speed of relaxation depend upon the first one: the speed and efficiency of recovery depend upon the second.

The production of lactic acid during contraction, which is probably the ultimate cause of the mechanical response, must be regarded as being very sharply localized within the muscle fibre. Its sudden appearance probably changes the electrical and colloidal state of certain sensitive protein interfaces in the muscle, producing a rise of tension and the phenomena of contraction. During relaxation, a process just as important as contraction though largely neglected by physiologists, the acid is removed from its place of action through neutralization by the alkaline buffers of the muscle. The physical problem of how the acid produces the contraction has not yet been solved, but whatever be the mechanism, its reversal in relaxation would appear to be due simply to the withdrawal and neutralization of the acid whose presence locally in high concentration evoked the response. This affords a simple explanation of the delayed relaxation associated with fatigue: the neutralization of lactic acid has rendered the muscle less alkaline, and further neutralization is slower and less effective.

D. The Efficiency and Speed of the Recovery Process

(which will be referred to further in Section N below) appear to depend upon the condition of the muscle. The 'efficiency' may be measured by the ratio (total lactic acid removed) : (portion of lactic acid oxidized), as found in oxidative recovery. In the experiments of Hartree and A. V. Hill (17) this ratio appeared to vary from 4.9:1 to 6:1, with a mean of about 5.5:1; in Meyerhof's experiments (35, 36) it was about 4:1; in the former experiments the supply of oxygen was adequate, the muscles were never fatigued, and recovery was rapid; in the latter the contrary was the case and recovery was correspondingly less efficient. It would seem probable that the efficiency of recovery in a healthy trained man is at least as high as in an isolated frog's muscle; we shall assume therefore in what follows a figure of 6:1 for the ratio

(total lactic acid removed) : (lactic acid oxidized)

in the recovery process of a healthy normal man.

In the isolated muscle the 'speed' of recovery is best measured by experiments on the recovery heat production (17). Like that of all chemical reactions it depends on the temperature, increasing 2 to 3 times for a rise of 10°C. It increases rapidly with the oxygen pressure. It increases with the magnitude of the effort from which recovery is necessary. It depends presumably upon the catalytic oxidative activity of surfaces inside the living cell. The oxygen pressure in the muscle increases in man with the vigour of the circulation and

the efficiency of the lungs. Moreover, the oxidative activity of a cell may be changed in various artificial ways, e.g. it may be diminished by narcotics or cyanides (Warburg (44)). It is natural therefore to assume that the velocity of oxidative recovery in human subjects may vary similarly—not only in accordance with the oxygen supply, but with the more intimate physico-chemical characteristics of their muscle cells.

E. *The Production of Lactic Acid in Man.*

After severe exercise lactic acid appears in the urine (Ryffel (42)). The amount however is small, and is no measure whatever of the quantity which has appeared in the body. The most obvious tokens of the latter are (a) the magnitude of the oxygen debt, and (b) the increased respiratory quotient, following severe exercise. It would seem probable that carbohydrate alone provides the energy for the excess metabolism of exercise: this certainly appears to be the case in isolated muscle (33). In moderate, prolonged, steady exercise therefore, in which the concentration of lactic acid attains a steady value in the muscle, the respiratory quotient approximates to unity. As soon, however, as the exercise reaches a severity greater than can be maintained on a contemporary supply of oxygen—as soon as the level of exercise is reached at which lactic acid must continue to accumulate throughout it—the respiratory quotient rises above unity, CO_2 is turned out by lactic acid, sodium (or potassium) lactate being formed from the bicarbonate of blood and tissue fluids. In our observations the extreme upper value of the apparent respiratory quotient (R.Q.) of the excess metabolism, after exercise, has been 2.6: assuming a real respiratory quotient of 1, this means that for every gramme-molecule of O_2 being used, and for every gramme-molecule of CO_2 being produced, 1.6 gramme-molecules of CO_2 were being turned out by lactic acid from bicarbonate.

Now in moderate exercise the main part of the lactic acid liberated in the muscle does not combine with bicarbonate. This is clearly shown in Section M below, and can be substantiated on the isolated muscle. The heat produced in the process of relaxation (as found by Hartree and Hill (15)) is far larger than that corresponding to the neutralization of lactic acid by bicarbonate, and Meyerhof (38) has suggested that the neutralization associated with relaxation is effected by the buffered alkaline proteins of the muscle tissue itself, according to the scheme, (lactic acid) + (sodium protein salt) \rightarrow (sodium lactate) + (acid protein). This corresponds exactly to what we believe to be the mechanism by which acid is neutralized (and CO_2 carried) in blood (39), and is capable moreover of providing adequate heat. Thus, in moderate exercise, the protein buffers of the muscle should be capable of neutralizing all the acid formed, little CO_2 should be driven out, no dyspnoea should occur, and the R.Q. of the excess metabolism should remain at unity. In severe exercise, on the other hand, an excess of lactic acid is produced for which the supply of protein buffers is inadequate, the hydrogen-ion concentration rises, the respiratory effort increases,

and CO_2 is turned out of bicarbonate in muscle and blood. Hence the R. Q. rises above unity, its rise being an index of the amount of acid combining with bicarbonate. On the qualitative side therefore—by the examination of the urine after severe exercise—we know that lactic acid is produced in man and escapes in small quantities into the blood: on the quantitative side, the very great rise of the R. Q., during and after violent effort, is a sign that the acid production is considerable. In the next section we shall show how the 'oxygen debt' may be used as an indicator of the absolute amount of lactic acid present in the body at the end of exercise.

F. *Lactic Acid and Oxygen Debt.*

The 'oxygen debt' is defined as the total amount of oxygen used, after cessation of exercise, in recovery therefrom. It may be measured in man in the following simple manner. Firstly, the resting rate of oxygen intake of the subject is determined by the Douglas bag method in some standard position (standing, sitting, or lying). The exercise is then taken. Immediately on its cessation the subject begins to breathe from the air into a large Douglas bag, remaining at rest in the standard position throughout recovery. We have used bags of capacities 400, 300 and 200 litres. If one bag be not sufficient, a second one may be used and two analyses made. In experiments described in Section H, on the time-course of recovery, a series of bags was employed, in fairly rapid succession throughout the recovery period, and such experiments have told us how long it is necessary in general to collect the expired gases. After moderate exercise the oxygen intake will return to its resting level in about 6 to 8 min.: after very severe or exhausting exercise it may remain high for a much longer time. The total oxygen used in the selected recovery period is then determined by analysis and measurement in the usual manner. From this is subtracted the oxygen which the body would have used in the same time at rest. The difference represents the oxygen debt at the end of the exercise.

There are four possible objections to this method: (a) At the end of exercise a certain amount of oxygen is lacking, which at rest is dissolved or combined in blood or tissues, and this quantity is included in the figure determined as above. It can be calculated, however, that this error is almost negligibly small, at any rate in the case of oxygen debts of several litres. (b) One cannot be sure that the oxygen intake has returned to normal, after a selected period of recovery, unless special observations be made to prove that it has. This objection is admitted. The error, however, is always in the same direction, viz. in that of making our observed oxygen debt too small: we have endeavoured always to allow an adequate recovery period, and in some observations (see Section H below) we have followed the rate of oxygen intake throughout. We can claim anyhow that our observations are certainly not too large. (c) The oxidations of recovery may replace in part the normal resting oxidative processes: e.g. if part of the resting metabolism be due to the necessity of producing heat to keep the body warm, this part could safely be omitted by the body during recovery from exercise, when loss of heat, rather than its

production, may be important. This objection also is valid. The error however cannot be very large, and in any case it will cause our observations again to be too low, so that again we may claim them as minimum values. (d) Part of the oxygen debt observed may be due to the excessive movements of heart and respiratory muscles occurring during recovery: these movements, however, rapidly slacken, and cannot in any case account for more than a small fraction of the considerable oxygen debts found, especially after they have slackened. On the whole, therefore, we may regard our results as reasonably accurate statements of the oxygen required in the metabolic processes of oxidative recovery.

No process is known to occur in muscular exercise in man which is not apparent in isolated muscle, and we shall now assume that the recovery oxygen, measured as above, is used entirely in the oxidative removal of lactic acid. The oxidation is as follows: $C_3H_6O_3 + 3O_2 \rightarrow 3CO_2 + 3H_2O$. Now, if the 'efficiency' of recovery be assumed to be six in the sense defined above, i.e. if a total of six molecules of lactic acid disappear in recovery for every one oxidized, then six molecules of lactic acid will be removed for every three molecules of oxygen used, or two gramme-molecules of lactic acid (i.e. 180 grm.) for every gramme-molecule of oxygen (i.e. 22.2 litres). This means that an oxygen debt of 1 litre betokens the presence in the body, at the end of exercise, of about 8.1 grm. of lactic acid. The following table gives the magnitude of the oxygen debt, at the end of various types of exercise, in several different individuals, together with the total lactic acid content of the body calculated therefrom:

TABLE I.

Subject.	Weight Kilos.	Exercise.	Oxygen Debt. c.c.	Total Lactic Acid. grm.
H	73	Flat running at speed of 191 metres per min., for 5 min. 8 secs.	1668	13.5
H.	—	Flat running at speed of 201 metres per min., for 4 min. 18 secs.	2485	20.1
H.	—	10 secs. violent jumping with skipping move- ment	2510	20.3
H.	—	20 secs. violent jumping with skipping move- ment	5504	44.6
H.	—	Flat running for 3 min. 23 secs. at a speed of 239 metres per min., i.e. at a speed causing an increasing debt of oxygen	2870	23.3
H.	—	Flat running for 33 min. at a speed of 239 metres per min. Practical exhaustion	7890	64.0
L.	65	36 secs. violent jumping with skipping move- ment	5700	46.2
L.	—	Flat running at speed of 261 metres per min. for $4\frac{1}{2}$ mins.	7160	58.0
L.	—	Jumping over stool 14 inches high for 2 min. 7 secs.	10499	85.0
W. M. H.	72.5	Violent gymnastic exercises for 30 secs. involv- ing rapid contractions of all the muscles, leading to exhaustion	7670	62.1
		Ditto preceded by a rapid $\frac{1}{4}$ mile run	13250	107.2
S.	68.55	Ditto for 30 secs.	6455	52.3
M. W.	79.9	Ditto for 32 secs.	7810	63.3
W.	—	Flat running, 225 yds. in 23.4 secs.	8745	71.0

We see therefore that large quantities of lactic acid may be produced in the body, certainly up to 1.5 gm. per kilo of body weight. The extreme rapidity with which it can be produced is notable, as is shown by the last entry in the table, where over 3 gm. per sec. were being liberated by a powerful individual running 225 yds. at top speed. Even moderate exercise, such as running at about 7 miles per hour, leads to the production of about 13 gm. of acid in the body. It must not be supposed that this lactic acid occurs only in the absence of oxygen. There is a balance, even at rest, between lactic acid being produced and lactic acid being removed, as will be shown in Section I, dealing with the 'steady state'. The more vigorous the exercise the higher the level of the lactic acid at which the balance occurs, and the greater the oxygen debt at the end of exercise. If, however, the severity of the exercise be too great the supply of oxygen cannot cope with the production of lactic acid, no balance is attained, and exhaustion rapidly sets in.

G. *The Lactic Acid Maximum and the Limit of Muscular Exertion.*

Stimulation of the isolated muscle leads to a so-called 'stimulation' or 'fatigue' maximum of the lactic acid content, which was supposed at one time (14, 21) to depend upon a limit in the amount of the lactic acid precursor. This, however, is not the case. Meyerhof has shown (37) that the immersion of the muscle in a solution of alkaline phosphate buffers may considerably increase the stimulation maximum of lactic acid. Apparently the limit is set by the rise in the hydrogen-ion concentration (cH) effected by the presence of the lactic acid itself, and may be increased if the rise of cH be hindered by the presence of extra alkali. This is a very important observation, as we shall see below, in explaining the differences in maximum effort between different human subjects. It was found also by Meyerhof that the stimulation maximum is practically the same for indirect as for direct excitation: his values range from 0.24 per cent. to 0.43 per cent. Let us assume that a human subject, as the result of a supreme effort, can produce some 0.3 per cent. of lactic acid in all the active muscles involved in violent running, jumping, or skipping. These muscles, in an active 70-kilo man, might weigh about 25 kilos: this figure of course is necessarily a matter of estimation. The total acid present therefore would amount to 75 gm. Hence, if the recovery removal of 8.1 gm. of lactic acid be secured by the intake of 1 litre of oxygen, the oxygen debt in this case of extreme effort should amount to $75/8.1 = 9.3$ litres. Table I above contains several observations on the oxygen debt found in cases of severe and exhausting exercise. Thus H. running for 33 min. at a rate at which the oxygen requirement exceeded the maximum oxygen intake produced a debt of 7,890 c.c.; M. W. performing violent rapid gymnastic exercises produced in 32 secs. a debt of 7,810 c.c.; W. as the result of a rapid sprint of 225 yds. in 23.4 secs. produced a debt of 8,745 c.c.; L. by violent jumping for 2 min. 7 secs. caused a debt of 10,499 c.c.; W. M. H. by an extreme effort a debt of about $13\frac{1}{2}$ litres. The

prediction therefore is verified; the oxygen debt in these cases attains a value corresponding reasonably well to that calculated from the fatigue maximum of lactic acid in the muscles. It is clear that in such efforts the limit is not placed at an early stage by fatigue occurring in the nervous system, but rather by the presence of acid in the muscles themselves.

Different individuals, even those apparently of similar muscular development, differ enormously from one another in the vigour and duration of their maximum efforts. There are two types of effort: (a) the violent and short-lived type not depending on concurrent oxidation, and (b) the more moderate, longer lasting type, depending on the supply and utilization of oxygen, i.e. made possible by contemporary and adequate recovery. All possible stages intermediate between these may occur. These individual differences, important in everyday life, in athletics, and probably in medicine, are of a complex nature. The withdrawal of protective nervous inhibitions, the mental and moral factors ('guts') which make one individual inevitably a better man than another, are clearly of importance; the excitability of the respiratory centre, and of the nervous system as a whole, the size and capacity of lungs and heart, the fitness of various organs to stand the strain of violent effort, have all clearly to be taken into account. There remains, however, one simple chemical factor, the efficiency of buffering of the muscles, which determines the fatigue maximum of lactic acid, the maximum oxygen debt, and therewith the extent and duration of a short-lived violent effort. This factor is fully considered in Section M below.

H. *The Rate of Oxidative Recovery from Exercise in Man.*

There are only a few investigations recorded in physiological literature of the rate of return of the oxygen intake to its resting value on the cessation of exercise. Campbell, Douglas, and Hobson (5) followed the return to the normal resting value for periods of 80 and 90 min. following different rates of exercise on a bicycle ergometer. Krogh and Lindhard (26) performed similar experiments using similar apparatus.

Our experiments, which have been concerned with the influence of varying the type and severity of the exercise on the time relations of recovery, have confirmed the earlier observations, and have brought out certain other points of interest. Many types of exercise have been employed, of which the following may be regarded as typical: (a) flat running at a speed of 211 metres per min. (8 miles an hour), the time relations of recovery being determined (i) after a short period of exercise (4 min.), and (ii) after a long period (22 min.); (b) flat running at a speed of 250 metres per min. (9.3 miles an hour), continued for 6 min.; (c) rapid violent jumping with a skipping movement, continued for 36 secs.

Previous to the exercise the resting respiratory exchange was determined in some standard position (usually sitting). The subject finished the exercise

in front of a stand carrying a wide pipe with nine projecting tubes. To one of these tubes the valves and mouthpiece were fixed: to the others were attached rubber bags through single-way stop-cocks. All the tubes were of $\frac{3}{4}$ inch bore, the apparatus being similar in principle to that used by Campbell, Douglas, and Hobson (5). The subject, on cessation of exercise, adopted the standard resting position, adjusted the valves and nose-clip, and commenced to expire into the first bag. At the end of about $\frac{1}{2}$ min. (end of nearest expiration) the first bag was turned off, and the second one turned on for a like interval. This process was continued, the intervals of collection being gradually increased. After the eighth bag the valves were attached successively to separate bags, if the recovery was being followed for longer periods.

Table II gives the results obtained in three typical experiments.

TABLE II.

Exp. 1. Subject, L. Exercise, flat running at 211 metres per min. for 4 mins. Resting (sitting): O₂ intake, 251 c.c. per min.; CO₂ output, 227 c.c. per min.; R. Q., 0.91. Total oxygen used in recovery in 24 min. = 2,837 c.c. Oxygen requirement at this speed 2,790 c.c. per min.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen:	
		Total in Interval.	per min.
33.3 secs.	16.7 secs.	1096	1975
35.2 "	51 "	416	709
35.6 "	1 min. 26.3 "	229	386
1 min. 3.2 "	2 " 15.7 "	238	226
2 " 3.3 "	3 " 49 "	333	162
2 " 6.1 "	5 " 58.6 "	86	41
3 " 7.4 "	8 " 30.4 "	259	83
3 " 4.1 "	11 " 36.1 "	64	21
5 " 6.1 "	15 " 41.2 "	82	16
5 " 35.8 "	21 " 2.2 "	34	6

Results shown in Fig. 1.

Exp. 2. Subject, L. Exercise, violent jumping for 36 secs. Resting (sitting): O₂, 243 c.c. per min.; CO₂, 197 c.c. per min.; R. Q., 0.81.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen:	
		Total in Interval.	per min.
33.7 secs.	17 secs.	1105	1969
33.1 "	50 "	761	1382
32.3 "	1 min. 23 "	463	860
1 min. 5.2 "	2 " 11.7 "	554	514
1 " 3.6 "	3 " 16.1 "	368	347
2 " 3.3 "	4 " 49.6 "	536	261
4 " 2 "	7 " 52.2 "	633	157
6 " 31.2 "	13 " 8.8 "	743	114
6 " 33 "	19 " 41 "	537	82

Exp. 3. Subject, L. Exercise, flat running for 6 min. at 250 metres per min. Resting (sitting): O₂, 262 c.c. per min.; CO₂, 211 c.c. per min.; R. Q., 0.81. Oxygen requirement for this speed, 5,360 c.c. per min. Actual max. excess

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intake, 3,483 c.c. per min. Hence a rapidly increasing oxygen debt, amounting to 7,160 c.c. at the end of 6 min. running.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen:	
		Total in Interval.	per min.
33.5 secs.	17 secs.	1542	2763
36 "	52 "	927	1548
35.1 "	1 min. 28 "	502	858
1 min. 1 "	2 " 15 "	568	559
2 " 3.5 "	3 " 48 "	642	312
2 " 4.2 "	5 " 51 "	418	202
3 " 6.3 "	8 " 27 "	533	172
4 " 12 "	12 " 26 "	436	104
4 " 2.7 "	16 " 13 "	344	85
5 " 2.3 "	20 " 46 "	479	95
5 " 4.8 "	25 " 49 "	254	50
5 " 4 "	30 " 53 "	182	36
5 " 2.7 "	35 " 56 "	283	56
5 " 4.7 "	40 " 59 "	51	10

Results in Fig. 1.

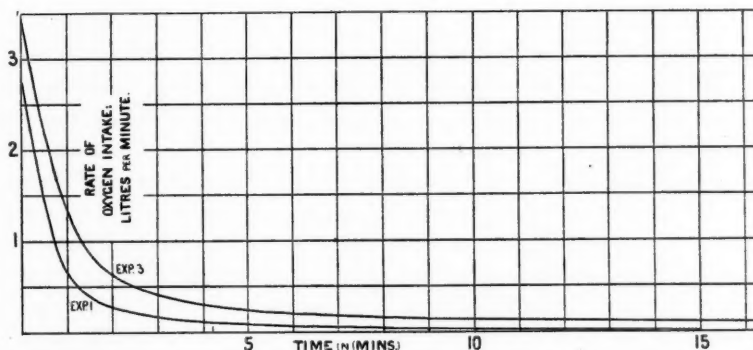


FIG. 1. Oxygen intake during recovery. Horizontally, time from cessation of exercise; vertically, rate of oxygen intake in excess of standing. The lower curve, falling rapidly to the base line, represents recovery from a short bout of moderate exercise. The upper curve, falling less rapidly, represents recovery from a rather longer bout of much more strenuous exertion.

The results indicate that on cessation of the exercise there is an immediate rapid fall in the oxygen intake, which occurs both after severe and after moderate exercise. This rapid fall is complete within 6 to 8 min. If, however, the exercise was severe, the oxygen intake falls to a level somewhat above the original resting level, the excess being maintained for prolonged periods, depending on the severity and extent of the exercise. There is thus a difference between the curves obtained—(a) after moderate exercise carried out for a short time, and (b) after severe or extended exercise. Even in moderate exercise, where the oxygen supply is adequate, if the exercise be maintained for a long period there is a prolonged recovery, and the total oxygen in the recovery period is larger in amount than in the case where the same exercise is maintained only for a short period. Now since, in such exercise, the heart, lungs, and circulation are all able to cope with the demands of the

muscles for oxygen, the only debt for oxygen should be that produced at the beginning of the exercise, i.e. before the respiratory, circulatory, and oxidative mechanisms have attained the rate of working equivalent to the exercise. The only explanation of the increased debt, after a prolonged period of such moderate exercise, appears to be that when the exercise is prolonged the steady maintained concentration of lactic acid, corresponding to the rate of oxidation as in Section I below, causes gradual diffusion of the acid to points distant from the oxidative recovery mechanism of the muscle (e.g. into lymph and other tissues), from which it returns by diffusion only very slowly to be oxidized in recovery. The exhaustion resulting from long-continued, comparatively moderate exercise is to be attributed therefore to the presence, outside the muscles, of noticeable quantities of lactic acid, the oxidative removal of which occurs only very slowly, as the acid diffuses gradually back—under a low concentration gradient—to the oxidative mechanism inside the fibre.

I. *The 'Steady State' in Exercise.*

In this section we shall deal with recovery occurring during the exercise itself. In prolonged steady exercise a balance must be struck between break-down and restoration, the rate of break-down being determined by the vigour of the exercise, that of restoration (*a*) by the concentration of lactic acid in the active muscles, and (*b*) by their oxygen supply. We shall consider here the characteristics of the dynamic equilibrium attained during steady exercise.

It was shown recently by Hartree and Hill (17) that the total magnitude of the recovery process is proportional, as was to be expected, to the extent of the 'initial' break-down preceding and initiating it. They showed also, in a muscle in oxygen, that the velocity of this recovery process is increased—not only absolutely but relatively—by an increase in the effort from which recovery is necessary. Thus, given a constant oxygen pressure in the muscle, the rate at which recovery occurs increases very rapidly as the break-down from which recovery is necessary is increased. In other words, oxidation is more rapid the greater be the concentration in the muscle of the bodies—e.g. lactic acid—whose removal constitutes recovery. This is the chemical law of 'Mass Action'. In human muscular exercise the process is more complex: here we have an oxygen pressure in the muscle which decreases to some degree as the amount of exercise increases, so tending to diminish the rate of oxidation: for severe continued exercise this limit to the oxygen supply is the predominant factor and will be further considered below; for moderate exercise, however, where the oxygen supply is adequate, we may expect the rate of oxidation in the muscle to increase continuously as the concentration of lactic acid in it is increased. When muscular exercise is taken in man at a constant speed the lactic acid content of his active muscles increases gradually from its resting minimum at the start. This rise in lactic acid content increases the rate of oxidation, so that finally, if the oxygen supply be adequate, a 'steady state' is reached in which the rate of

lactic acid production is balanced by the rate of its oxidative removal, and its concentration remains constant in the muscle as long as exercise at that speed is maintained. Hence, the rate of oxygen consumption should rise continuously during the exercise, from its resting minimum at the start to a steady value depending on the severity of the effort; here it should be maintained throughout the exercise. Conversely, when the effort terminates, the lactic acid should continue to be oxidized, but at a decreasing rate as its concentration falls, so that the rate of oxygen consumption should fall continuously from its steady exercise value to its original resting minimum. The latter phenomenon we have discussed in Section H above. These expectations are well verified in certain experiments we have made on the rise in the rate of oxygen intake after

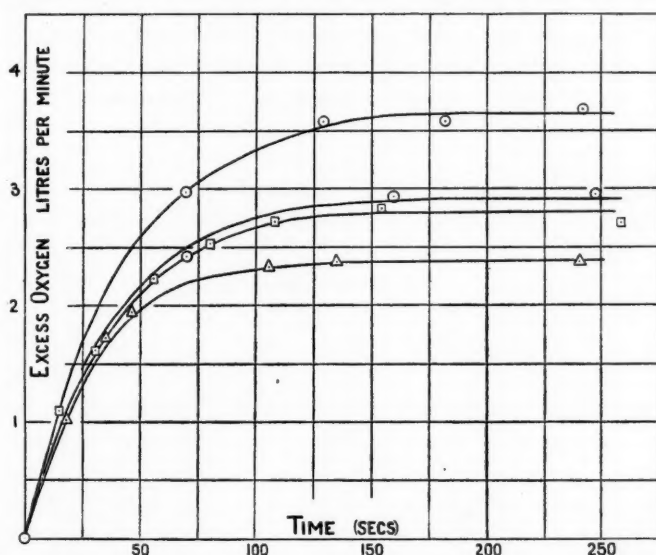


FIG. 2. The attainment of a 'steady state', in running at various constant speeds. Horizontally, time from commencing to run; vertically, rate of oxygen intake in excess of standing. Speeds of 181, 203, 203, and 267 metres per min. The lower three curves represent a genuine steady state, the uppermost curve only an apparent steady state in which the oxygen intake is at its maximum and the oxygen debt is rapidly increasing.

the beginning of exercise. In these experiments the subject started to run, at a given constant speed, around a circular grass track $92\frac{1}{2}$ yds. ($84\frac{1}{2}$ metres) in circumference. The subject (H.) is a practised runner and was able to maintain constancy of speed for long periods, especially with the aid of a timekeeper calling out (and recording) the times of successive laps. He carried a small Douglas bag with a side pipe (much more convenient for running than a top pipe), a three-way tap, and a mouthpiece fitted with rubber valves. During each run the expired air was collected in the bag for a period of about 30 secs., the tap being turned on and off at the end of suitable expirations, the exact interval being recorded by the timekeeper on signals from the runner. During running, respiration is so rapid and free that a 30-sec. sample is quite adequate,

as is seen from the consistency of the points in Fig. 2. After a sufficient interval of rest (about 10 or 12 min.) for the oxygen consumption to return to its resting level, the run was repeated, and the expired air collected in a different 30-sec. interval. In this way a series of observations can be made on the rate of oxygen intake at various moments during the process of 'warming up' to the steady state represented by the final constant level of exercise. In Fig. 2 each result, expressed as the rate of oxygen consumption per minute due to the exercise (i. e., after subtraction of the resting rate), is plotted as the ordinate against an abscissa representing the time, measured from the commencement of running, of the *middle* moment of the interval during which the expired gases were collected. The curves show that the rate of oxygen intake due to the exercise in this subject rises rapidly from the start, reaching its final exercise value in 100 to 150 secs., and half its final value in about 25 secs. Further details of the experiments are given in the following table. The ventilation of the lungs at the highest speed is notable, especially when account is taken of the hindrance offered by valves and mouthpiece.

TABLE III.

Subject H. O₂ and CO₂ in c.c. dry and at N.T.P. Ventilation in litres per min. moist and at 37° C., and at the actual atmospheric pressure. S = standing.

Speed: Metres per min.	Mid-point of Sample: secs.	O ₂ per min.	Excess Oxygen due to Exercise, per min.	CO ₂ per min.	CO ₂ / O ₂	Total Ventila- tion.
181	S	269	—	248	0.92	9.16
	47	2220	1943	1780	0.80	48.7
	106	2618	2341	2242	0.86	56.1
	135	2652	2375	2405	0.91	59.3
	240	2655	2378	2622	0.99	67.8
	S	285	—	261	0.92	9.3
203	S	372	—	304	0.82	11.26
	70	2792	2420	2250	0.81	62.1
	159	3300	2928	3010	0.91	76.75
	247	3320	2948	2990	0.90	82.1
	362	3205	2833	2905	0.91	84.7
	S	306	—	259	0.88	10.18
203	15	1406	1096	1300	0.92	37.46
	31	1933	1623	1616	0.84	45.3
	56	2548	2238	2095	0.82	52.7
	80	2846	2536	2370	0.83	57.2
	108	3030	2720	2618	0.86	62.7
	154	3140	2830	2890	0.92	67.7
	258	3012	2702	2870	0.95	69.4
	S	315	—	275	0.87	10.3
	S	373	—	328	0.88	11.84
267	69	3340	2967	3310	0.99	87.6
	129	3950	3577	4040	1.02	114.0
	182	3950	3577	4360	1.10	132.6
	242	4055	3782	4335	1.07	138.4

So far we have discussed a genuine steady state of exercise in which the lactic acid concentration of the muscle attains a constant value, and the subject would be able (apart from extraneous disturbances, such as blisters on the feet) to continue the exercise almost indefinitely. This was almost certainly the case in the experiments recorded in the three lower curves of Fig. 2. In the highest

curve, at a speed of about 10 miles per hour, it was quite certainly not the case for the subject of our experiments, carrying the bag, pipes, and tap, and breathing through valves: he would manifestly have been unable to continue at this speed for more than 10 min., if so long. In such severe exercise the lactic acid is continuously accumulating in the muscles, the maximum oxygen intake (depending upon the capacity of heart and lungs) being inadequate to maintain the recovery at a level high enough to cope with the production of lactic acid. Hence, in such cases, the fact that the intake of oxygen has reached a constant value within $2\frac{1}{2}$ min. represents nothing more than the fact that its *maximum* level has been attained: *it does not imply that the body has reached a state of dynamic equilibrium in which break-down is balanced by recovery.* Considering the case of running, there is clearly some critical speed for each individual, below which there is a genuine dynamic equilibrium, break-down being balanced by restoration, above which, however, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in. The absolute magnitude of the maximum oxygen intake will be considered below.

The failure to realize the true nature of the steady state of exercise and its dependence on the maximum oxygen intake has led to some curious and paradoxical results. It is obvious that if the oxygen and energy consumption associated with a given type of exercise be required, it is necessary to continue it until a genuine steady state is attained. In running, the true oxygen consumption corresponding to a given speed can be measured only after the subject has been running at that speed for about $2\frac{1}{2}$ min. If, moreover, the exercise be so vigorous that a steady state is impossible, the rate of oxygen consumption corresponding to the exercise can be measured only by adopting a technique which we will describe later (Section K). The value actually attained is only the *maximum oxygen intake* for that type of exercise, and may not correspond in the least to the oxygen *requirement* of the body: in such a case what we require is (oxygen income) + (rate of increase of oxygen debt), and in severe exercise this cannot be measured directly by such means as we have described hitherto. An amusing paradox in this connexion has been recorded by Liljestrand and Stenström (28). These observers recorded the oxygen intake during horizontal running, and found that the oxygen consumption (per metre travelled) *decreased* as the speed increased over the range 140 to 300 metres per min. It was apparently more economical to run fast than slow! Now the opposite is notoriously the case, and these observations of Liljestrand and Stenström (of which, on technical grounds, we have no criticism) obviously need an explanation. The explanation is simple: the subjects of their experiments were not in a genuine steady state at the higher speeds. In the case, e.g., of their subject N. S. ((28), p. 183) it is clear that the maximum oxygen intake of about 3.3 litres per min. was attained at a speed of about 186 metres per min. Hence, however fast N. S. ran above this speed he did not use more oxygen, not because he did not require it, but because he could not get it. Consequently, since he

ran more metres per min. at the higher speed, the apparent oxygen consumption, i. e. the oxygen intake *per metre*, diminished as the speed increased. The real fact is that the true oxygen requirement per metre (as distinguished from the oxygen intake) increases continuously as the speed of running increases.

The finite time occupied in the attainment of the maximum oxygen intake allows an interesting comment on a well-known practice in athletics, viz. that of running the first part of a middle or long distance race very rapidly. For example, the times of the winner for successive laps ($\frac{1}{4}$ mile) in the mile race of the 1890 Oxford and Cambridge Sports were 80 secs., 93 secs., 88 secs., and this represents only partially the speed at which the first few hundred yards are run in a half-mile or mile race. The advantage of a high initial speed is that it rapidly raises the oxygen intake and the recovery oxidation to their maximum values. The speed at which a race is run depends upon—(a) the maximum oxygen debt, and (b) the amount of oxidation possible during the race. Clearly the more rapidly the oxygen intake can be pushed up to its limiting value, the greater will be the maximum effort that can be made.

J. *The Maximum Oxygen Intake.*

In this section we will consider shortly—(a) the factors in exercise which cause a high oxygen requirement, and (b) those which facilitate a high oxygen intake. We shall then give experimental values of the oxygen intake, considerably higher than have been recorded before, and shall discuss shortly the bearing of these values on the problem of the vigour and efficiency of the circulation in man.

Running on the flat is a form of exercise peculiarly well adapted to a high oxygen intake, and specially subject to a high oxygen requirement. As regards the *oxygen intake*, the body is free, respiration is unimpeded, movements are considerable and very rapid, and the muscles are rigid during only a small fraction of the cycle of each step; consequently there is very little hindrance to a free and rapid circulation of the blood, while the extensive and frequent movements of the limbs, together with an unimpeded and rapid respiratory cycle, assist largely in the venous flow of blood back to the heart. These factors are not so potent in the case of exercise of the types of swimming, rowing, and gymnastics. For example, Lindhard (31) has shown that in the severe effort of holding the weight of the body with arms bent, there is little excess oxygen intake during the exercise, fatigue comes on rapidly, and the excess oxygen consumption occurs mainly after the exercise is over. The circulation through the active muscles is impeded by their continued rigidity.

In *oxygen requirement*, as distinguished from *intake*, running also takes first place among types of muscular exercise. Running consists of rapid, vigorous alternating movements, each maintained only for the minimum of time. Experiments on the heat-production of isolated muscles have shown that, to set up a contraction in a muscle and to maintain it, both require a certain liberation of energy (16), while other experiments (22) have shown that in man the maintenance of the contraction is far less expensive than its setting up,

that indeed to maintain a contraction for 5 secs. requires only as much energy as to set it up initially. Hence it may be calculated that to make four steps in a second, as in running 100 yds. at top speed, should require more than three times as much energy as to set up a maximal contraction in the same muscles and to maintain it for a second. This calculation of course is very rough, but it illustrates the reason why rapid vigorous alternating efforts require far more energy than equally vigorous maintained ones. The setting up of a contractile effort in a muscle is much more expensive than its maintenance. In running, the efforts are almost entirely dynamic, and therefore expensive; in rowing, the cycles are much less rapid, and the effort of maintaining the contraction provides a much larger part of the whole expense, which is correspondingly smaller. The fatigue associated with maintained contraction is due, not to its expensiveness, but to the difficulty placed in the way of an adequate oxygen supply by the rigidity of the muscle.

Very many observations have been made by physiologists of the maximum oxygen intake in man, and in the following table we give a selection of the highest values:

TABLE IV.

Oxygen Intake during Exercise (Maximum Values).

Subject.	Reference.	Exercise.	Oxygen, c.c. per min.
L. Zuntz	(1)	Bicycling	2310
Kolmer	(1)	Swimming	2320
Durig	(1)	Climbing	2245
Kolmer	(1)	"	2660
Ranier	(1)	"	2580
Reichel	(1)	"	2670
M. A. M.	(1)	Bicycling (15 min.)	3000
M. A. M.	(1)	" (70 min.)	2850
Douglas	(2)	"	2795
Hobson	(2)	"	2680
Douglas	(2)	Pushing motor bicycle up hill	2940
Haldane	(2)	"	2790
Boothby	(2)	"	2750
J. J.	(3)	Bicycling (4 min.)	3200
J. L.	(3)	" (3 min.)	2550
V. M.	(3)	" (4 min.)	2520
N. S.	(4)	Running	3500
G. L.	(4)	"	2570
E. S.	(4)	"	2904
N. S.	(4)	Skiing	3750
G. L.	(4)	"	2800
E. S.	(4)	"	3480
N. S.	(4)	Skating	3060
E. S.	(4)	"	2530
N. S.	(5)	Swimming	2800
G. L.	(5)	"	2080

(1) Benedict and Cathcart, *Publication No. 187, Carnegie Institution of Washington*, 1913.

(2) Campbell, Douglas, and Hobson, *Phil. Trans., B.*, 210 1920, p. 1.

(3) Lindhard, *Pflügers Arch.*, 1915, clxi. 318.

(4) Liljestrand und Stenström, *Skand. Arch. f. Physiol.*, 1920, xxxix. 167.

(5) *Ibid.*, p. 1.

Thus running, skiing, and skating take the highest places in the series, all of these, in the accomplished performer, being types of exercise in which rapid

and violent alternating movements occur. Even the notoriously exhausting effort of pushing a motor bicycle up a hill does not approach them in its actual oxygen consumption! We have made a number of observations on various individuals running, some of which considerably exceed the values given in the above table; the following are well-substantiated maximum values:

Subject.	Age: Yrs.	Weight: Kilos.	Oxygen: c.c. per min.
S.	—	—	3985
W.	19	72	3995
J.	21	77	4040
L.	21	65	3535
H.	35	73	4175

All the subjects of the above experiments are of athletic disposition; none, however, are first-class athletes. S. is a University Rugby footballer, W. is a good short-distance runner, J. could probably be a first-class mile runner if he tried, H. is a practised runner (see section L), and L. is a well-built athletic person. In comparing these results with those in the previous table we must remember, also, that N. S. weighed 81 kilos, so that, reckoned per kilo, our numbers are still higher than those previously recorded. It is obvious, therefore, that up to about 4,175 c.c. of oxygen per min. can be taken in during running by a man of 73-kilo body-weight.

Let us consider what this means in circulation of the blood. Assuming a normal oxygen capacity of his blood, viz. 0.185 c.c. of O_2 per c.c. of arterial blood, and a utilization coefficient of 60 per cent., an oxygen intake of 4,175 c.c. per min. implies a blood-flow of $4.175/0.185 \times 0.6 = 37.6$ litres per min. Lindhard (30) in severe exercise found a utilization coefficient of $57\frac{1}{2}$ per cent. when his subject J. J. was taking in 2,410 c.c. of O_2 per min., and of 79 per cent. when he himself was using 2,550 c.c. per min., while he states that the mean of all his higher experiments was 67 per cent. His subject V. M. gave a value of 58 per cent., and a mean for higher experiments of 51 per cent. Even if a utilization coefficient of 80 per cent. be assumed in our experiments, the blood-flow corresponding to an oxygen intake of 4,175 c.c. must have been 28 litres a minute. During such exercise the brain and other relatively inactive parts of the body are being liberally supplied with blood, and the mixed venous blood can scarcely have been 80 per cent. unsaturated: neither is it likely that the arterial blood was completely saturated. It would seem fairly certain, therefore, that in running the blood-flow may attain a value between 30 and 40 litres per min., an enormous amount which it is difficult to realize more effectively than by turning it into gallons (8 to 10) and inquiring how long an ordinary water-tap would require to pass the same amount. It is obviously impossible to be a runner without possessing a powerful heart.

Other investigators have measured the circulation-rate by more exact methods. Meakins (32) found values at rest round about 8 litres per min., and during bicycle ergometer exercise about 17. Similar values were found by Douglas and Haldane (8). Liljestrand and Lindhard (29) found considerably

smaller values at rest. Lindhard (30) found up to 20 litres per min. during work. It would be difficult or impossible to measure the circulation-rate during vigorous running by such methods as these authors employed, and one is constrained to fall back on the rougher method of calculation given here, a method previously suggested by Y. Henderson and Prince (18); this method, however, shows values, during running, which are unquestionably higher than have ever been recorded in another type of exercise. We have made no exact observations of the pulse-rate during such running: it is not, however, extremely rapid, so that the output per beat in running must be exceptionally great. This is probably due to a good venous return.

That these large outputs can be maintained for a considerable time was shown by the experiment of Benedict and Cathcart (3 b) on their subject M. A. M., who for 15 min. maintained, while bicycling, an oxygen intake of 3,000 c.c. per min., and for 70 min. one of 2,850 c.c. Their subject was very exhausted by the longer effort. To maintain such an oxygen consumption for a long time while running is, however, quite easy, and the following experiment shows a much higher one. The subject (H.) ran at a steady speed of 240 metres per min. (9 miles per hour), carrying a large Douglas bag and breathing through valves and mouthpiece. At intervals the equipment was discarded and the expired gas sampled and measured, while the subject continued running at the same speed. The gradual rise in oxygen consumption is probably to be attributed to a painful blister on the foot causing inefficient movement.

Experiment.

Interval of collection.	Mid-point of interval from start.	Oxygen intake, c.c. per min.	CO ₂ output, cc. per min.	$\frac{\text{CO}_2}{\text{O}_2}$	Total ventilation, litres, moist and at 37° C.
75 secs.	3 min. 3 secs.	3590	3420	0.95	90
63 secs.	10 min. 48 secs.	3785	3800	1.0	100
77.5 secs.	17 min. 54 secs.	3910	3910	1.0	108
63 secs.	26 min. 32 secs.	3910	3930	1.0	118

This oxygen intake must have required a total blood-flow of not much (if any) less than about 30 litres per min., and it was maintained for half an hour. In a highly trained athlete it is obvious that still higher values must be possible.

It is open to question whether the oxygen intake is limited by the heart or by the lungs. It is possible that, at the higher speeds of blood-flow, the blood is only imperfectly oxygenated in its rapid passage through the lung; on the other hand, the limit may be placed simply by the sheer capacity of the heart. It would seem probable that, in the healthy normal man, both factors work together. A diminished oxygen tension in the coronary blood-supply, owing to the shortness of its stay in the capillaries of the lung, would lower the output of the heart itself, so tending to diminish the flow and to drive the oxygen tension up again. In abnormal persons one factor or the other may preponderate.

K. The Relation between Speed and Oxygen Consumption in Running.

The effect of speed on the oxygen intake during horizontal walking has been investigated by a variety of authors, and their results have been fully

summarized by Benedict and Murchhauser (3a). Similar determinations during 'level and grade walking' have been recorded recently by Monmouth Smith (43). The effects of speed upon the oxygen intake during walking, running, swimming, skating, and skiing have been investigated by Liljestrand and Stenström (27, 28). We have made a number of observations on the actual oxygen *intake* during running, over as wide a range of speeds as possible; since, however, at the higher speeds, a genuine steady state is never attained (as pointed out in Section I above), we have amplified these observations by others in which the oxygen *requirement* of the exercise is determined by a different method.

In determining the rate of oxygen intake during running at various speeds, the subject ran (as in Section I) with a constant measured velocity around a grass track, carrying a Douglas bag, and breathing through mouthpiece and valves, the tap being turned to allow the expired air to escape into the atmosphere. After continuing this for a time known, from the experiments of Section I, to be sufficient for the oxygen intake to attain a steady value, the tap was turned for a measured interval (usually about 1 min.) to allow a sample of expired air to be collected in the bag, the running being continued at the same speed. After the end of the interval the running ceased, and the measurement and analysis of the expired air were carried out in the usual manner. Experiments were made at a variety of speeds, and on several subjects (which amply confirm one another), and in Fig. 3 the curve A summarizes the observations of the excess oxygen intake made on our most usual subject (H., aged 35, weight 73 kilos, vital capacity 5 litres, normal resting pulse-rate about 60, in fair general training owing to a daily slow run of about one mile before breakfast). It must not be supposed that this line represents accurately the same subject's excess oxygen intake when running without the respiration apparatus, which provided a small but appreciable hindrance, especially at the higher speeds: probably when unhampered he is noticeably more efficient, and might, with freer respiration, attain a rather higher oxygen intake. It is seen that the rate of oxygen intake per minute due to the exercise, i.e. in excess of standing, increases as the speed increases, reaching a maximum, however, for speeds beyond about 260 metres per min. (9.7 miles per hour). However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation, and the diffusion of oxygen to the active muscle-fibres have attained their maximum activity. At the higher speeds the requirement of the body for oxygen is far higher, but cannot be satisfied, and the oxygen debt continuously increases.

Curve A of Fig. 3 expresses the relation between speed and oxygen *requirement* (as distinguished from *intake*) only at speeds of less than about 210 metres per min. (7.8 miles per hour), where the body can attain a genuine steady state. At higher speeds the same relation can be investigated by another method, not involving the attainment of such a steady state. The procedure measures the total *excess oxygen intake during, and in recovery from, a given muscular effort of short duration*. The subject stands for some minutes, ready

to run and breathing through the apparatus, his expired air escaping to the atmosphere, until his standing resting minimum oxygen intake is likely to be reached. He turns the tap, causing the expired air to flow into the bag, and immediately proceeds to run a given distance (say 100 yds.) at a measured speed. At the end of the run, and for the succeeding 10 or more minutes (the interval required depending on the magnitude of the recovery), he stands breathing into the bag until recovery is expected to be complete, the total

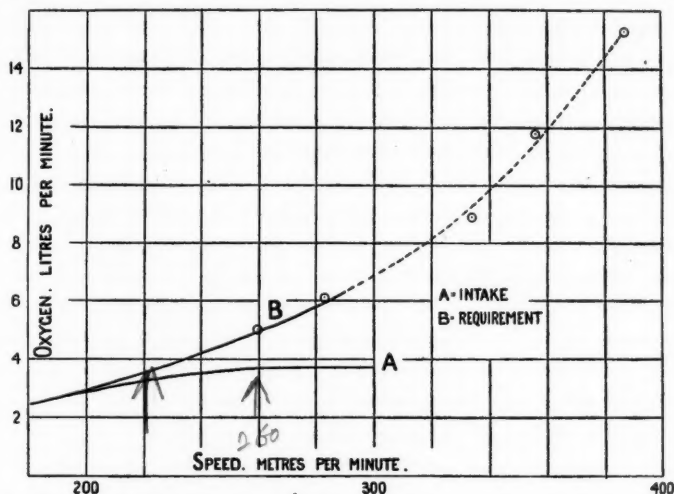


FIG. 3. Relation between oxygen intake (curve A), or oxygen requirement (curve B), and speed, in running at various speeds. The circles on curve B, and the dotted curve through them, were obtained indirectly by a calculation described in Section L.

interval of collection being measured. The total oxygen intake during this interval is then determined in the usual manner, and from this is subtracted the amount of oxygen which would have been used in the same time, *had no exercise been taken*. The difference gives the total oxygen consumption caused by the exercise, during the run and in recovery therefrom. Suitable observations of the standing resting oxygen intake are made before, and sometimes after the run. The following example illustrates the procedure:

Subject, H. Resting (standing): O_2 , 346 c.c. per min.; CO_2 , 277 c.c. per min.; R. Q., 0.80. *Exercise:* ran $1\frac{3}{4}$ laps (148 metres) in 30.5 secs., breathing into bag from start. Speed, 291 metres per min. Interval of collection, 8 min. 5 secs. Total oxygen used, 5,950 c.c.; resting (standing) value, same interval, 2,795 c.c.; difference due to exercise, 3,155 c.c. Hence oxygen requirement at this speed = 6,200 c.c. per min.

Here no assumption is made that a steady state of any kind has been attained: the only assumption indeed is that the excess oxygen intake is to be credited to the exercise. This method has been used to measure the real oxygen requirement of running at various speeds, and the result of our experiments are shown in curve B (unbroken portion), Fig. 3. It is seen that the

oxygen requirement rises continuously, at an increasing rate, as the velocity increases, attaining enormous values—far beyond the possibility of satisfying them contemporaneously—at the higher speeds. The curve B diverges from the curve A beyond about 220 metres per min.: at lower speeds they are the same. In H., carrying the respiration apparatus, all speeds greater than 220 metres per min. imply an increasing oxygen debt, with gradually oncoming exhaustion caused by the accumulation of lactic acid. At high speeds the accumulation of acid is rapid, the oxygen requirement exceeding considerably the maximum oxygen intake.



These methods and results might bear some application to the case of persons whom metabolic, cardiac, or other disturbances have rendered incapable of prolonged exercise, of any but the mildest type. By walking or running a short given distance, or indeed by any standard given effort, the oxygen requirement of that effort could be determined, without any assumption of the attainment of a steady state, and compared either with the value found in normal man or with the maximum oxygen intake attainable or allowable for the abnormal individual in question.

The curve of Fig. 3 really represents what we may call the 'efficiency' factor in running. A man may fail to be a good runner by reason of a low oxygen intake, a low maximum oxygen debt, or a *high oxygen requirement*; clumsy and uneconomical movements may lead to exhaustion, just as well as may an imperfect supply of oxygen.

L. Distance and Speed in Athletics.

The results of the preceding section have an interesting application to athletics. The subject H. was able ten years ago, with a maximum effort, to run the following distances in the following times, i.e. at the following speeds:

Distance.	$\frac{1}{4}$ mile.	$\frac{1}{2}$ mile.	$\frac{3}{4}$ mile.	1 mile.	2 miles.
Time	53 secs.	1 min. 17 secs.	2 min. 3 secs.	4 min. 45 secs.	10 min. 30 secs.
Average speed, metres per min.	455	419	392	333	306

This considerable variation of speed with the duration of the effort can be explained quantitatively by considerations of oxygen supply alone. Let us assume that his maximum oxygen intake per minute, in excess of standing, was 4.0 litres (i.e. 0.2 litres greater than it is now), and that his maximum oxygen debt was 10 litres (i.e. about the maximum recorded in this paper). Let us further assume that at the end of the race his oxygen supply, actual and potential, was completely exhausted. Then in a race lasting for 1 min. the total oxygen available would be $(10+4) = 14$ litres, i.e. for 1 min. he could run at a speed requiring 14 litres of oxygen per min. In a race lasting 5 min., however, the total oxygen would be $(10+5 \times 4) = 30$ litres, i.e. for 5 min. he could run at a speed requiring $30/5 = 6$ litres per min. Thus in the longer

race the speed must be considerably reduced. On these lines the following table may be calculated:

Distance.	$\frac{1}{4}$ mile.	$\frac{1}{3}$ mile.	$\frac{1}{2}$ mile.	1 mile.	2 miles.
Average speed, metres per min.	455	419	392	339	306
Total oxygen potentially available	13.5	15.1	18.2	29.0	52
Oxygen requirement per min.	15.3	11.8	8.9	6.1	4.95



This table gives us immediately a relation between speed and oxygen requirement, which we may compare with that given, for the same subject, in Fig. 3 above. Before doing so, however, we must note that the respiration apparatus used in the experiments recorded in Fig. 3 offered a definite, if small, hindrance to movement, and we may allow for this provisionally by assuming that, for a given oxygen requirement, the speed is reduced 15 per cent. by the apparatus carried. Hence, if we reduce all the speeds in the above table by 15 per cent. we obtain the following set of numbers, which are shown as circles in Fig. 3 above:


Distance.	$\frac{1}{4}$ mile.	$\frac{1}{3}$ mile.	$\frac{1}{2}$ mile.	1 mile.	2 miles.
Speed (reduced for respiration apparatus)	387	356	334	283	260
Oxygen requirement per min.	15.3	11.8	8.9	6.1	4.95

We see that the last two of these calculated quantities lie close to the curve actually observed for H., while the first three appear to make a good continuation of it. We have been unable hitherto to continue the observations on H. at the higher speeds, owing to the smallness of our track making faster running on it impossible. There can be little doubt, however, that if the observations were made they would lie close to the values calculated as above: a few isolated observations on other subjects at higher speeds confirm the general rise of the curve. Hence, we may conclude that *the maximum duration of an effort of given intensity is related to the intensity in a manner depending simply upon the supply of oxygen, actual or potential, i.e. upon the maximum rate of oxygen intake and the maximum oxygen debt of the subject in question.* This is a striking confirmation, from another aspect, of the truth of the principles discussed in this paper. It would appear to be of importance in the scientific study of athletics and physical training, both in health and in disease.

M. *The Importance of Tissue Buffers in Muscular Effort.*

In recent years the fundamental part played by the buffers of the blood, in respiration and muscular exercise, has been very fully discussed. The importance, however, of the buffers present in the muscles themselves has been largely neglected, partly owing to their relative inaccessibility to investigation, partly because of a failure to realize the magnitude of the neutralization process occurring in the muscles during exercise. Moreover, the study of buffers, and of the principles governing their behaviour, has been somewhat obscured by a logarithmic notation of hydrogen-ion concentration, which has made even the comparatively expert feel that there is something unduly subtle in their

action. As a matter of fact, given an elementary knowledge of the principles governing the behaviour of electrolytes in solution, the action of buffers is extremely simple and intelligible, and since it is of the utmost importance to an understanding of muscular activity, of respiration, of dyspnoea, and the like, we have given below a rather full discussion of the subject. We have avoided throughout the use of the logarithmic notation (pH), as leading only to obscurity, and have dealt with the simple and intelligible conception of the hydrogen-ion concentration itself, for which we have adopted the usual symbol cH. As a prelude, we may state that the action of a buffer in solution consists merely in the substitution of a weak acid for a strong one, the strong acid in the case of muscle being lactic acid, the weak ones being carbonic acid, phosphoric acid, and protein.



If a very small quantity of strong acid be added to pure water, or to a neutral salt solution, e.g. of NaCl, a very large change in the hydrogen-ion concentration (cH) results. For example, at 22°C. the cH of pure water is 10^{-7} grm.-ions per litre (i.e. one ten-millionth part of a milligramme of ionic hydrogen per c.c.): if now 1 c.c. of normal hydrochloric acid, containing 36.5 mg. of HCl, be added to a litre of such water, the cH rises ten thousand times, to a value of 10^{-3} . According to our observations, some 90 grm. of lactic acid may be liberated in the body as the result of severe exercise. Dissolved in 60 litres of water this amount of lactic acid would produce a cH of about 1.5×10^{-3} ; the cH of blood is about 4×10^{-8} ; thus the result of exercise, in the absence of some mechanism able to eliminate this effect of added acid, would be to raise the cH of the body fluids some 40,000 times. Actually the change of cH is very small: the maintenance of bodily processes, in particular of respiration, and of the physical state of the colloidal proteins of the tissues, demands an extremely high constancy of cH: this constancy is maintained by the 'buffers', both of blood and tissues. As Ritchie (41) has shown, the change of cH of an isolated muscle on moderate stimulation is almost inappreciable.

Weak acids, e.g. carbonic acid H_2CO_3 , boric acid H_3BO_3 , phosphoric acid H_3PO_4 (in its second and third dissociations), amino-acids, and in particular proteins such as haemoglobin or those of muscle (which act as acids at the cH of the body), are only very slightly dissociated into hydrogen ions and anions. Calling such a weak acid HA, the reaction $\text{H}^+ + \text{A}^- \rightarrow \text{HA}$ goes almost entirely to the right. Now, in the body many such weak acids exist, but normally they are largely in the form of their sodium or potassium salts, NaA or KA, which are fairly highly ionized into Na^+ (or K^+) and A^- ions. Now imagine that we add a strong acid, e.g. HX, ionized largely as H^+ and X^- , to a solution of such a salt of a weak acid, the following mixture is obtained: $\text{Na}^+ + \text{A}^- + \text{H}^+ + \text{X}^-$. But the acid HA is an extremely weak one, i.e. the ions H^+ and A^- cannot exist side by side in appreciable concentrations, they must form the undissociated acid HA. Hence, provided the buffer salt NaA be present in sufficient excess, practically all the H^+ is removed by the reaction

$H^+ + A^- \rightarrow HA$, leaving only the neutral or approximately neutral salt Na^+X^- and the excess of buffer salt Na^+A^- . Thus the buffer salt has, so to speak (and this is the origin of the term 'tampon', mistakenly translated 'buffer'), 'absorbed', or 'mopped up', the hydrogen ions of the added acid, and turned them into undissociated weak acid and approximately neutral salt. Such buffers are extremely effective, reducing the change of cH caused by added acid many thousands or even tens of thousands of times. In the body the most effective buffer salts are bicarbonates, phosphates, proteins, and particularly haemoglobin.

The matter can be expressed in another way. Buffer salts may be regarded as stores of sodium (or potassium). An added acid requires sodium to neutralize it: the stronger acid seizes sodium from the weaker; if the anion of the buffer salt were that of a strong acid the effect would be *nil*, one strong acid would be exchanged for another; actually, however, the buffer is a salt of a very weak acid, and the strong added acid is replaced, therefore, by a neutral salt and a very weak acid, which raises only slightly the cH of the solution.

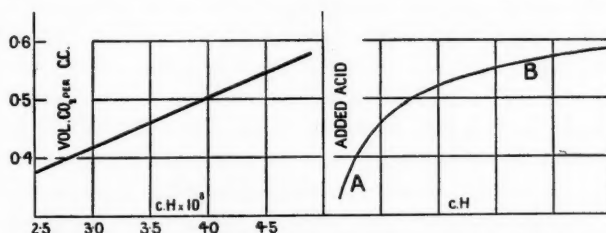


FIG. 4. Curves showing the 'efficiency of buffering'. Horizontally, hydrogen-ion concentration (cH); vertically, acid (or CO_2) added to attain that cH. Left, actual curve for blood. Right, hypothetical curve for muscle.

The quantity of acid which must be added to a solution to change the cH by a given amount may be used to measure the efficiency of buffering of that solution, to that acid, at that cH. For example, the efficiency of buffering of blood, to carbonic acid, can be deduced from the left-hand diagram of Fig. 4. The relation between vCO_2 (the total volume of CO_2 held by 1 c.c. of blood in solution and combination) and cH is there given as a straight line, and the slope of this line represents the efficiency of buffering: the greater the slope the more efficiently the blood is buffered; if it were not a straight line the efficiency of buffering at any cH would be given by the slope of the tangent to the curve at the corresponding point. The study is still in its infancy, but there can be no doubt of the existence of similar buffer curves for lymph, tissue fluids, and living muscle substance; the efficiency of buffering of these determines the amount of lactic acid which can be taken up without fatigue or exhaustion, without escape of unneutralized acid into the blood, and corresponding excessive respiration. This buffer curve is probably represented by a line such as that in the right-hand diagram of Fig. 4. To produce a given change in cH the quantity of added acid is largest at the start, and becomes less and less as the cH of the solution increases, so that the efficiency of buffering (as measured by

the slope of the curve) is greatest at first, and becomes less and less as more and more acid is added. If now the resting condition of a muscle be represented on the curve by a point such as A, then considerable violent exercise can be taken and noticeable quantities of acid produced, without much disturbance of the cH, and therefore without much fatigue in muscles or distress in respiration. If, however, the resting condition of the muscle be represented on the curve by a point such as B, the efficiency of buffering will be less, the effects of exercise and acid production will be relatively greater, and distress will rapidly ensue. Moreover, if the muscle were to start at a resting state such as A, it might, as the result of exercise and lactic acid production, pass along the curve to B; here the effects of further exercise and of further acid production would be relatively more severe, owing to the less efficient buffering at B than at A. This additional effort might lead to far more than the corresponding additional distress.

Lactic acid compared with an acid such as HCl is fairly weak: its dissociation constant is given as 1.38×10^{-4} at 25°C . It is, however, a very much stronger acid than carbonic acid, for which the dissociation constant (at 37°C .) is about 6×10^{-7} : than leucin (3.1×10^{-10}) and other amino-acids: than haemoglobin (oxy-, 6×10^{-7} , and reduced, 7.5×10^{-9} ; see (4)) and other proteins: than phosphoric acid in its second and third dissociations (2.1×10^{-7} and 5.6×10^{-13}). Indeed a 0.1 per cent. solution of lactic acid in water is about 10 per cent. ionized. In the body, therefore, *lactic acid will never occur as such: it will always obtain base from some weaker acid to form sodium, potassium, or ammonium lactate, in which forms alone it will exist in muscle, lymph, and blood.* This is borne out by the fact that the reaction of isolated muscle never becomes appreciably acid, even in severe fatigue. The consequence, however, is that exercise, liberating lactic acid, increases the concentration of these other weaker acids in the muscles and body fluids; hence, owing to the presence of these other weaker acids, the cH does actually rise, though much less than it would in the absence of buffer salts. One only of these other weaker acids, viz. carbonic, is volatile; hence an immediate after-effect of a short burst of severe exercise is to drive off excessive quantities of CO_2 . This fact has appeared in the work of other authors, e.g. Krogh and Lindhard (26), and Campbell, Douglas, and Hobson (5). It is shown more vividly by the first experiment given in Table V below, where the apparent respiratory quotient of the excess metabolism produced by exercise is as high as 2.6 two minutes after a very violent effort: in other words, for every CO_2 molecule produced by oxidation, another 1.6 molecules were being displaced by lactic acid. It is obvious that CO_2 driven out by lactic acid will have to be restored later if the lactate formed at its expense be oxidized or removed. (If, however, the lactate were excreted by the kidneys, it might appear in the urine as sodium lactate, so depriving the body of sodium and preventing a corresponding amount of CO_2 from being restored later.) Hence, at some later stage in recovery, we find that the apparent respiratory quotient of the excess metabolism falls far below unity—indeed it may become negative—as also has been found by previous

Oxygen debt
of hemostatics
and D.A.H.

authors (3*b*, 26, 5), but is shown more clearly in the second experiment quoted. It is obvious that, in the later stages of recovery, such a very low value of the apparent R. Q. cannot represent a genuine metabolic change: it is due simply to the restoration of CO₂ driven away earlier by lactic acid.

TABLE V.

Exp. 1. Subject, L., 3 hours after meal. Exercise, jumping with rapid skipping movement for 36 secs. Room temp., 14° C. Resting resp. exchange (sitting, before exercise, for 10 min.): oxygen, 243 c.c. per min.; CO₂, 197 c.c. per min.; R. Q., 0.81. The expired gases were collected during successive intervals, one bag being turned on at the instant the previous bag was turned off. All gases in cubic centimetres at N. T. P.

Interval of collection.	Mid-point of interval from end of exercise.	Recovery excess oxygen:		Recovery excess CO ₂ :		Apparent R. Q. of excess metabolism.
		per min.	Total in interval.	per min.	Total in interval.	
min. secs.	min. secs.					
33-7	17-0	1969	1105	2763	1551	1.40
33-1	50-2	1382	761	2448	1350	1.77
32-3	1 23	860	463	1863	1001	2.17
1 5-2	2 12	514	554	1343	1460	2.62
1 3-6	3 16	347	368	828	879	2.39
2 3-3	4 50	261	536	598	1229	2.29
4 2-0	7 52	157	633	292	1178	1.86
6 31-2	13 9	114	743	135	880	1.19
6 33-0	19 41	92	537	79	567	0.86

By 'excess oxygen' and 'excess CO₂' are meant the amounts taken in or given out over and above the resting sitting values.

Exp. 2. Subject, L., 3 hours after meal. Exercise, horizontal running round grass track at 9½ miles per hour, maintained for 4½ min. Temp. 16° C. Resting resp. exch. sitting: oxygen, 262 c.c. per min.; CO₂, 211 c.c. per min.; R. Q., 0.81. Rate of oxygen intake during exercise, measured after 2 min. 48 secs. of exercise, 3,745 c.c. per min.: rate of CO₂ output, ditto, 3,755 c.c. per min. Oxygen requirement of exercise, measured as on p. 157 above, 5,360 c.c. per min. The vigour of the exercise, therefore, was considerably in excess of that corresponding to the maximum oxygen intake, and a heavy oxygen debt was incurred.

Interval of collection.	Mid-point of interval from end of exercise.	Recovery excess O ₂ :		Recovery excess CO ₂ :		Apparent R. Q. of excess metabolism.
		per min.	Total in interval.	per min.	Total in interval.	
min. secs.	min. secs.					
33-5	17	2763	1542	2984	1666	1.08
36	52	1548	928	2189	1313	1.42
35-1	1 28	858	502	1507	881	1.76
1 1	2 15	559	568	1079	1097	1.93
2 3-5	3 48	312	642	568	1170	1.82
2 4-2	5 51	202	418	292	604	1.45
3 6-3	8 27	172	534	230	714	1.34
4 12	12 26	104	437	79	332	0.76
4 2-7	16 13	85	344	44	178	0.52
5 2-3	20 46	95	479	33	166	0.35
5 4-8	25 49	50	254	-1	-5	-0.02?
5 4-0	30 53	36	182	-11	-56	-0.31?
5 2-7	35 56	56	282	25	126	+0.45?
5 4-7	40 59	10	51	-12	-61	-1.20?

The values denoted with queries (?) are doubtful because of the smallness of the quantities involved.

TABLE V (continued).

Exp. 3. Subject, H., 10 hours after meal. Exercise, easy horizontal running round grass track at 7.6 miles per hour. Temp., 13° C. During recovery (standing) for 7 min. 2 secs. following 4 min. 10 secs. exercise, the total excess oxygen used (over and above standing) was 2,485 c.c. and of CO₂ excreted was 2,508 c.c.: R. Q. of recovery metabolism = 1.01. The oxygen debt, therefore, was relatively small, and the recovery R. Q. can be sufficiently explained by the oxidation of carbohydrate.

Conditions.	Oxygen intake :		CO ₂ output :		R. Q.		Ventilation : litres* per min.
	c.c. per min.	Excess over standing.	c.c. per min.	Excess over standing.	of total.	of excess.	
Basal (bed)	217	—	195	—	0.90	—	6.1
Standing before exer- cise	306	—	269	—	0.88	—	10.2
Standing after exer- cise	315	—	275	—	0.88	—	10.3
During exer- cise (after 4 min.)	3012	2702	2870	2598	0.95	0.96	69.0

* Moist, at 37° C., and at 754 mm. Hg pressure.

Moderate continued exercise in man does not lead to this driving off of CO₂, as is shown by Exp. 3 above. Apparently when lactic acid is formed in moderate amount during exercise its neutralization is effected by the protein buffers of the muscle, and possibly in part by phosphates, but not by the bicarbonates present in blood and tissue fluids; hence there is no dyspnoea, and the R. Q. of the excess metabolism remains at or near that of carbohydrate. This is confirmed by recent work on isolated muscle, in which (17) the total heat-production in the initial anaerobic phase of contraction can be attributed to simple causes, (a) the break-down of glycogen into lactic acid, and (b) the neutralization of that acid, provided only that we may assume the neutralization to take place by protein buffers and not by phosphates or bicarbonates. The heat of neutralization of acid, as shown by Meyerhof (38), is large if it be effected by protein buffers, but small if it be effected by others. Hence in an unfatigued muscle we must assume a protein salt to be the neutralizing agent; only when the supply of suitable protein buffer has run out, and when the pH inside the muscle has risen far enough, may we suppose the lactic acid to attack the bicarbonate, and so to drive off CO₂: it is probably at this stage that laboured respiration begins.

Little is known about the buffers of the muscle, more is known about the buffers of the blood. In blood the buffers are bicarbonates and phosphates, serum proteins and haemoglobin. All the serum proteins are capable, to a small degree, of acting as buffers; there is strong evidence, however, that one protein only, haemoglobin, is a really effective agent in neutralizing added CO₂, and its effectiveness appears to be enhanced by its confinement within the semi-permeable walls of the blood corpuscle (7). The efficiency of haemoglobin

as a buffer is really due to the fact that as an acid it is extremely weak. Moreover reduced haemoglobin is a weaker acid than oxyhaemoglobin (4) and should correspondingly be a better buffer: Christiansen, Douglas, and Haldane (6) found that reduced blood takes up appreciably more CO_2 than oxygenated blood at the same CO_2 pressure. Now it is obvious that human individuals may differ enormously from one another in the degree to which their muscles can tolerate sudden and violent exercise, and the same individual will vary enormously from time to time. A sudden effort which will make one man exhausted and stiff and lead to extreme dyspnoea will not affect another, or the same man when he is in better training. This is doubtless partly a matter of the buffers in the blood: lack of haemoglobin, as in anaemia, may cause a much greater rise in cH for a given addition of acid or CO_2 (7); this, however, is not the sole cause, and the blood is only a small part of the total tissue fluids. Muscular stiffness may result, in a powerful individual 'out of training', from a few seconds only of severe exercise, at a time when his blood is quite reasonably normal in its buffering power. Indeed, it is continually observed that, even when in good training for running, moderate unaccustomed exercise, of the type (say) of climbing a rope in a gymnasium, may lead to severe stiffness in the muscles concerned in that process. It would appear that training is able somehow to increase the *local* buffering power of the muscle proteins, possibly by a relative increase in the amount of the salt of the *weaker* protein acids. The salt of the weaker acid is the more effective buffer; it will surrender more rapidly and readily its available alkali, and it will cause a smaller rise of cH when it has done so. If it be present only in small amount it will be used up first of all in neutralizing added acid: its rôle must then be taken on by some less effective agent, the efficiency of buffering will fall, and the cH will rise more rapidly as acid continues to be liberated. The excessive rise of cH so produced may cause a semi-permanent physico-chemical effect in the colloidal structure of the tissue, something analogous to precipitation or coagulation of some constituent, so leading to stiffness, pain, and loss of power in the muscle, and, by diffusion into the blood and lymph, to excessive respiratory movements and dyspnoea.

We shall consider later the question of oxidation in its bearing on this subject. By very violent exercise for a short time, even—or possibly particularly—in the best trained man, it is possible to exceed many times over any possible oxidative recovery during the exercise, and to produce enormous quantities of lactic acid in the muscles, so that fitness for short-lived effort denotes almost entirely the ease with which the acid products of activity can be dealt with *without oxidation*, i.e. through neutralization by the tissue buffers. It may denote, also, doubtless the relative immunity of the body at large to the harmful or painful effects of a sudden change of cH ; in the main, however, fitness for violent short-lived effort would seem to depend upon the quality of the tissue buffers. If this be the case, we may perhaps inquire why the body does not maintain the presence of the more effective buffers, i.e. of the

salts of the weaker protein acids, *all the time and independently of 'training'*. This inquiry lies within the province rather of the biologist than of the physical chemist, but there is no reason why the biologist should not inquire in physico-chemical terms. An answer may be suggested as follows: The more effective buffer is the less stable one, in so far as it is the salt of the weaker acid. The salt of a very weak acid readily surrenders its sodium, even to a weak acid, and as soon as it has done so it ceases to be a buffer. Hence in the less vigorous metabolic processes of the untrained or abnormal man, in the distorted processes of disease, or after excesses of meat or drink, the highly unstable and most efficient buffers may be partly saturated with other rather stronger acids, may surrender their sodium, and so become inoperative. A relatively unstable system has been displaced by a stabler, if less effective one, and can only be restored as a gradual adaptation to an external need. In the muscle there are buffers of all kinds, salts of stronger and of weaker protein acids, phosphates, and bicarbonates. The salts of the weaker acids may be transformed into their undissociated acids by chance acidic metabolic products, and even by an undue excretion of sodium or potassium by the kidney. Exercise, especially regular exercise, stimulating and regulating the oxidative and excretory functions of the cells, may protect the more unstable protein buffers from such acid contamination, and so lead to those three essentials of bodily fitness, (a) quickness of muscular response and relaxation, (b) immunity from fatigue, dyspnoea, and their unpleasant consequences, and (c) a high upper limit of the effort which can be made, beyond the range of a contemporary oxygen supply.

The subject of tissue buffers is at present of necessity speculative. A further study of the physico-chemical properties of muscle proteins, unchanged as far as possible by chemical or manipulative treatment, may throw much further light upon the problem of muscular effort, muscular stiffness, and dyspnoea. In applying such results to muscular exercise in man it is well to make a clear mental separation of the two great types of effort—(a) the sudden, violent, and anaerobic type, and (b) the long-continued type, involving contemporary oxidation. Short-lived, vigorous efforts are made almost entirely by the expenditure of 'capital', in the form of lactic acid production: long-continued, milder efforts by the expenditure of 'income', in the form of rapidly ensuing, almost contemporary oxidation. Thus short and violent exercise depends largely, if not mainly, on the ease with which lactic acid is dealt with by the tissue buffers; long-maintained exercise on the efficiency of oxidation, and the ease and liberality of oxygen supply.

N. *The Oxidative Factor in Muscular Fitness.*

An efficient oxidative metabolism will tend to maintain a low resting lactic acid minimum in the muscle, and probably to restrain the appearance of acid metabolites likely to neutralize the more efficient but less stable buffers of the

muscle substance. When the organism is subjected to a low oxygen pressure, the initial discomfort and muscular disability are doubtless to be associated partly with the lower oxygen pressure in the brain and heart, partly with the fact that the rate of oxidative recovery from exercise is diminished. In addition, however, it would seem probable that a reduced oxygen pressure, by slowing the last stages of recovery and by diminishing the resting oxidative break-down of waste products of metabolism, would decrease the efficiency of the most potent protein buffers of the muscle, and so lead to greater discomfort following a sudden effort. It would be of great interest, therefore, to ascertain the extent of the maximum oxygen debt—(a) at sea-level, and (b) at high altitudes, before and after acclimatization.

The chief oxidative factor in muscular effort is concerned, however, with its prolongation by means of a rapid and efficient recovery. The 'efficiency' of recovery we have discussed already above: it appears to change with the condition of the muscle, and may well vary from one individual to another. The rapidity of recovery depends upon a variety of factors, upon the oxygen supply and pressure, upon the temperature, and upon the *intrinsic oxidative power of the living cells*. It is usual to treat capacity for exercise, and freedom from the unpleasant symptoms of dyspnoea, as though they resided merely, or at any rate mainly, in the supply of oxygen through the lungs and circulation, and in the degree of buffering of the blood. Indeed, books and articles are written on respiration which take little or no account of the oxidative function of the cell, the mechanism thereof, and the factors which influence it. This is natural, in a sense, since so little is known about the oxidative mechanism. Something, however, is known, and a short discussion of the oxidative mechanism may be of interest here. It will emphasize how many possibilities there are in explaining the various abnormalities of response to exercise.

The oxygen supply to the active muscles in man, depending as it does on the efficiency of heart, lungs, and circulation, on the corpuscles, haemoglobin, and alkalies in the blood, on diffusion of oxygen in the tissues, and on the pressure of oxygen in the air, has been already the subject of innumerable investigations. We have been able to add little to these, beyond the experimental proof that the rate of oxygen supply can attain considerably higher values than had previously been supposed. Experiments with isolated muscles have made it clear, even apart from experiments on man, that the oxidative process of recovery is intimately dependent on the pressure of oxygen, increasing rapidly in speed as the latter is raised. Hence, even in moderate prolonged exercise, a vigorous circulation is advantageous in maintaining a higher average oxygen pressure in the active muscles, and so ensuring a lower level of the lactic acid in the final 'steady state' attained, with less resultant fatigue and smaller after-effects. A higher oxygen pressure would appear to be always an advantage. *It must be regarded, however, as merely antecedent, and contributory to the speed of the oxidative cell process itself.* Of this latter little can be said, because so little yet is known; with further research, however, it will almost

certainly prove to be the most important factor of all in facilitating and completing the cycle of muscular activity.

It might have been supposed that in man the speed of the recovery process depends simply upon the supply and the pressure of oxygen, that the muscle restores itself, with the oxidative removal of lactic acid, exactly as fast as the supply of oxygen enables it; if this were so the curves of Fig. 1 would represent merely the oxygen supply to the active muscles, falling gradually to its resting value on the cessation of exercise. The form of the curves makes this, *a priori*, very improbable; there is conclusive evidence, however, from another direction that it is definitely not the case; the oxidative recovery process has an intrinsic speed of its own, like other katalysed chemical reactions, even in the presence of a completely adequate supply of dissolved oxygen. Hartree and Hill (17), in recent experiments, have analysed the course of the recovery heat-production of

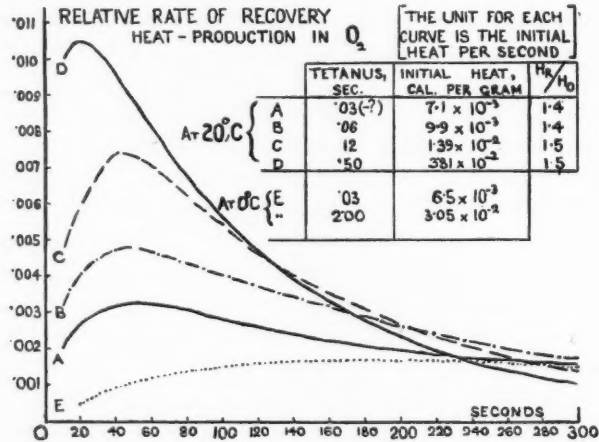


FIG. 5. Recovery heat-production of frog's sartorius muscles in oxygen.

a frog's sartorius muscle suspended in pure oxygen; here the amount of oxygen dissolved in the muscle itself must be far more than adequate to complete the oxidations of recovery from a short tetanic stimulus, so that no delay is interposed by the diffusion of oxygen to the places where it is required. In spite of this the recovery process is very protracted, as is shown in Fig. 5. In 5 min. at 20°C. recovery is by no means complete: at 0°C. it has barely attained its maximum speed. The rate of recovery increases rapidly as the temperature rises, but decreases rapidly as the pressure of oxygen falls. Hence, at 37°C. in man, with a comparatively low oxygen pressure in the active muscle, the rate of recovery is not far different from that in the frog's sartorius at 20°C. and in pure oxygen. The rate at which the chemical processes of recovery occur starts at a low level, rises to a maximum, and then slowly falls again to zero. Moreover, the greater the initial effort from which recovery is necessary, the greater is the relative (not merely the absolute) rate of that recovery. Here, in Fig. 5,

we are dealing with the intrinsic oxidative capacity of the cell itself, uninfluenced by any considerations of oxygen supply. The characteristics of these curves may guide us in the further analysis of the chemistry of the recovery metabolism of muscle.

Many factors are known to influence the speed of oxidative recovery; of these we have mentioned temperature and oxygen pressure, but there are other important chemical agencies which do the same. Cyanides prohibit oxidation (and therefore recovery) completely, even in minute doses. According to Warburg (44) this is due to the removal of traces of katalytic iron, by chemical combination with the cyanide, from its place of action in some formed constituent of the cell. Many narcotic substances hinder or prevent oxidation, probably (according to Warburg (44)) owing to their preferential adsorption to the same formed constituents of the cells. There is strong evidence, derived from a study of the red corpuscles of birds, that the solid parts of the cells are the seat of oxidation. Laking the red corpuscles barely diminishes their oxygen consumption: removal of the 'ghosts' of the laked corpuscles abolishes it entirely. Apparently oxidation takes place at the surfaces of such formed constituents of living cells, by adsorption of the oxidizable body, and through a reaction katalysed by traces of adsorbed iron. Narcotics displace the oxidizable body, cyanides remove the iron; both, therefore, hinder or prevent oxidation.

In another direction, recent work by Hopkins (25) has shown the existence in active cells of a chemical body ('glutathione') capable of katalysing oxidations by acting as a 'hydrogen acceptor', so enabling oxidation to occur without the direct and immediate utilization of molecular oxygen. The total quantity of this 'hydrogen acceptor' in muscle is probably very small, so that no appreciable amount of oxidation can occur without the aid of molecular oxygen: there is no possibility, for example, of the 'oxygen debt' in man being noticeably increased by such means. On the other hand, however, the speed and vigour of muscular oxidation may depend largely on the presence of an adequate quantity of such bodies, though the relative importance of this and other factors cannot, as yet, be assessed.

It is obvious, therefore, that—apart from temperature, and pressure of oxygen—there are many possible ways in which the rate of oxidation in a living muscle-cell could be altered. The surfaces, which are the seat of oxidation, might vary in their chemical or colloidal nature: preferential adsorption of bodies analogous to Warburg's narcotics might displace the proper food-stuffs, for example, in disturbances of metabolism; physical or chemical interference with the katalytic iron might diminish the rate of oxidation of the appropriate bodies, even when properly adsorbed; a decrease in the amount or activity of suitable hydrogen acceptors might weaken an essential link in the oxidative chain. These matters still are of necessity largely speculative, and we must wait for further improvements in knowledge of the physical chemistry of living cells. Little, however, is gained by regarding the phenomena of exercise,

respiration, and dyspnoea as simpler than they really are: further knowledge will certainly introduce these other factors.

We wish to express our sincere thanks to the various persons who have submitted themselves to our—often severe—experiments: their hearty goodwill and interest have made the investigation possible. We desire particularly to thank our colleague, Mr. C. N. H. Long, B.Sc., both for his skilled and strenuous activity as a subject, and for his help in the analysis of the results. We are much indebted also to Mr. Corker, of Messrs. C. Macintosh & Co. of Manchester, for his help in the design of suitable experimental bags for the collection of expired gases.

We are indebted to the Medical Research Council for grants to cover the expenses of the investigation.

An extremely good paper

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

FIFTEENTH ANNUAL GENERAL MEETING

THE FIFTEENTH ANNUAL GENERAL MEETING was held at Oxford on Friday and Saturday, April 21 and 22, 1922, at 10 a.m. in the University Museum.

The President, Professor O. J. Kauffmann, was in the chair.

The minutes of the last General Meeting were taken as read and confirmed. These minutes had been published in this Journal.

Election of President. Prof. Sir A. E. Garrod, K.C.M.G., M.D., F.R.S., was elected President for 1922-3. He took the chair in place of the retiring President, Prof. O. J. Kauffmann, and proceeded to move a vote of thanks to Prof. Kauffmann for his services as President during his year of office.

Election of Honorary Member. Prof. Kauffmann, the retiring President, was elected an honorary member of the Association.

The election of Officers, members of the Executive Committee, and new members followed.

Treasurer: Sir William Hale-White.

Secretary: Dr. H. Morley Fletcher.

Members for England:

Professor J. Hill Abram.
Dr. J. R. Charles.
Professor T. R. Elliott.
Professor W. E. Hume.
Dr. A. F. Hurst.
Sir Humphry Rolleston, K.C.B.

Members for Scotland:

Dr. E. Bramwell.
Professor G. L. Gulland.
Professor T. K. Monro.

Members for Ireland:

Dr. W. Boxwell.
Dr. H. L. McKisack.
Professor F. C. Purser.

New Members.

T. Izod BENNETT, M.D., Middlesex Hospital, W. 1. Assist. Phys. Middlesex Hospital.

J. Crichton BRAMWELL, M.B., Manchester Royal Infirmary. Med. Officer in charge of the Electro-cardiographic Department at the Manchester Royal Infirmary.

ASSOCIATION OF PHYSICIANS

Sir J. Charlton BRISCOE, Bart., M.D., 30 Harley St., W. 1. Phys. King's College Hospital.

S. B. BOYD CAMPBELL, M.D., 39 Wellington Park, Belfast. Assist. Phys. Royal Victoria Hospital, Belfast.

J. M. H. CAMPBELL, O.B.E., M.D., 8 Spa Mansions, Bermondsey. Medical Registrar, Guy's Hospital.

Richard C. CLARKE, O.B.E., M.B., 29 Victoria Square, Clifton, Bristol. Assist. Phys. Bristol Royal Infirmary.

Robert COOPE, M.D., 12 Falkner Square, Liverpool. Assist. Chemical Pathologist, Royal Infirmary, Liverpool.

Alexander GOODALL, M.D., 14 Walker St., Edinburgh. Assist. Phys. Royal Infirmary, Edinburgh.

A. Fergus HEWAT, M.B., 3 Darnaway St., Edinburgh. Assist. Phys. Royal Infirmary, Edinburgh.

F. J. NATTRASS, M.D., 44 Jesmond Road, Newcastle. Assist. Phys. Royal Victoria Infirmary, Newcastle-on-Tyne.

John PARKINSON, M.D., 1 Devonshire Place, London, W. 1. Assist. Phys. London Hospital.

R. L. Mackenzie WALLIS, M.D., 105 Harley St., London, W. 1. Lecturer on Chemical Pathology, St. Bartholomew's Hospital.

The Treasurer, Sir William Hale-White, then presented the annual financial report, which showed a satisfactory balance of £282 7s. 0d. The report was adopted.

A letter was read from Professor Gulland inviting the Association to meet in Edinburgh in 1923. The invitation was cordially accepted.

A letter from the Secretary (Mr. Frankau) of the Association of Surgeons had been received inviting the Association of Physicians to take part in a set discussion to be held in London in 1923 during the Annual Meeting of the Association of Surgeons. It was resolved that the Secretary of the Association of Physicians should write to Mr. Frankau declining the invitation as the Association of Physicians was meeting that year in Edinburgh and found it impracticable to hold another meeting.

SCIENTIFIC BUSINESS

FRIDAY, APRIL 21, 10 a.m. MORNING SESSION

1. Dr. A. R. Parsons recorded three cases of *Mikulicz's disease* occurring in Dublin. He regarded this condition as a syndrome, not as a clinical entity. It was met with in various degrees and might arise from different causes.

Dr. J. H. Drysdale supported the view that Mikulicz's disease should be regarded as a syndrome, and pointed out its common occurrence in lymphatic leukaemia.

Dr. Parkes Weber and Dr. French referred to its not infrequent association with syphilis.

Dr. Thursfield and Sir Thomas Horder joined in the discussion.

2. Professor A. J. Hall with Professor J. S. Douglas (introduced) related a case of *lymphadenoma* which, when first seen, was thought to be one of meningitis, and was treated with anti-meningococcal serum. The patient improved, but later pyrexia recurred: small superficial abscesses appeared in the axillae, and jaundice developed. The patient had been previously treated in a sanatorium for pulmonary tuberculosis. Post-mortem examination showed an old tuberculous scar at the apex of one lung and small abscesses in the lungs. The spleen, 11 oz., contained small infarcts and abscesses. The liver was large and permeated with whitish streaks and nodules. Microscopically the nodules showed typical lymphadenoma. Professor Hall had

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obtained the temperature chart kept during the patient's stay in the sanatorium. This showed a remarkable relapsing pyrexia of the Pel-Ebstein type. He had studied other recorded cases of this type and presented for purposes of comparison a series of temperature charts reduced to a small scale and covering long periods of time.

Sir Humphry Rolleston suggested that in such cases a certain amount of necrosis may occur in glandular tissues which by absorption of the necrotic material might bring about an anaphylactic condition. Pyrexia might also be caused by secondary infection.

Professor Gulland referred to a case with a ten-day periodicity of recurrent fever in which a daily blood-count was made. The polymorphonuclear increase during the pyrexial periods was in favour of some infective condition.

Sir J. Galloway regarded the periodic pyrexia as a specific phenomenon due to some specific infection.

Dr. Parkes Weber, Sir T. Horder, and Sir A. E. Garrod joined in the discussion.

3. Dr. W. T. Collier (introduced) related a case diagnosed as *Sternberg's variety of lymphadenoma* in a man of 34 years. The cervical lymph glands and the spleen were enlarged. There was irregular pyrexia and a slight leucopenia. The case was regarded as one of acute tuberculosis. Post mortem—small ulcers in intestine, one of which had perforated. The iliac lymph glands and head of pancreas were occupied by growth: liver contained small white nodules, but there were none in the spleen. Microscopically, the growth was granulomatous—probably Hodgkin's disease—it contained giant cells.

Dr. Parkes Weber agreed as to the diagnosis of the case.

Sir Humphry Rolleston would not agree that it was a case of Sternberg's disease or of lymphadenoma. He regarded it as a case of sarcoma of obscure origin.

4. Professor A. Hijmans van den Bergh described his tests for the presence of *bile pigment in the blood* and discussed the clinical importance of these tests in the differential diagnosis of jaundice.

Dr. MacNee gave a more detailed account of the technique of these tests and confirmed their great value in doubtful cases of jaundice.

5. Dr. T. Houston and Dr. J. C. Rankin on the *Dreyer and Ward flocculation test for the diagnosis and treatment of syphilis* gave the results obtained in a long series of cases and compared these with the results obtained by other methods. They regarded the Dreyer and Ward test as the most accurate of these.

Professor Dreyer made some observations on the test as applied to treatment. Professor Parsons also spoke.

3. Dr. C. Wilson related a case of *cyanosis in a girl*, the nature of which was undiagnosed during life. At 10 years she became fat and flabby and mentally slow. At 13 she had attacks of abdominal pain, and gradually acquired a deep purple tint. The blood was normal. She became increasingly breathless and fat, and at 16 years weighed 12 st. 10 lb. She died at 19. Post mortem—the liver was very small and looked like a mass of fibrous tissue. Microscopically it showed a monolobular cirrhosis.

Sir H. Rolleston suggested that it was a case of congenital syphilis, in which the liver and pituitary gland were affected.

Dr. Parkes Weber and Dr. H. Campbell also spoke.

2-3 p.m.

Professor Gunn (introduced) gave a demonstration in the Pathological Lecture Theatre on the effects of *cardiac stimulants*.

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Professor Hijmans van den Bergh gave a practical demonstration of his method for determining the presence of *bile pigments in the blood*.

By the kind invitation of the Delegates the members of the Association were taken over the Clarendon Press and given a demonstration of printing and other processes.

FRIDAY AFTERNOON. 3 p.m.

1. Dr. Starling gave statistics of the frequency of *endocarditis lenta* at Norwich before, during, and after the war. He had met with no cases in sailors. This type of cardiac disease appeared to be very prevalent amongst those who had served in the war, and to be rare amongst civilians. Men of the finest physique who had been subjected to great strain appeared to be specially liable.

Dr. Stobie (introduced) discussed the frequency of *endocarditis lenta* in Oxford during the years 1910-21. 1912 and 1920 were the years of greatest frequency.

Dr. Carey Coombs discussed the conditions predisposing to *endocarditis lenta*. He stated that in his series most of the cases occurring before the war were females; the mitral valve was that most frequently affected, and in 100 per cent. there was a history of rheumatic fever. Whereas after the war, the cases in the series were all males; 40 per cent. had a history of rheumatic fever, 20 per cent. had a syphilitic history, and in 90 per cent. the aortic valve was the one affected.

2. Professor Cowan and Dr. J. K. Rennie (introduced) gave the results of investigations of the post-mortem records of 81 cases of *chronic valvular disease*. Of these 37 (or 45 per cent.) presented evidence of an acute *endocarditis* as well, whilst 44 (55 per cent.) showed no signs of an acute infection. They did not agree that acute *endocarditis* was more prevalent after than before the war.

Sir Thomas Horder pointed out that cases of *endocarditis lenta* may present a picture of renal rather than cardiac insufficiency.

Drs. Ellis, Poynton, Stacey Wilson, and others joined in the discussion.

3. Professor F. R. Fraser described a method for producing *rapid digitalis effects by oral administration* in urgent cases of heart disease. He showed with the aid of charts that the action of digitalis is very rapid when the drug is given in one large dose. Two to three drachms of the tincture produce a marked effect in a few hours. He regarded this method as safer than the administration of strophanthin intravenously in urgent cases.

Professor Meakins also advocated caution in the use of strophanthin intravenously.

Dr. Emmanuel and Dr. Sutherland also spoke.

4. Dr. F. V. Cotton gave a communication on *clubbed fingers as a sign of infection in structural disease of the heart*. He showed that clubbed fingers were most frequent in aortic disease, and especially so in cases which showed evidence of infection.

Professor Fraser asked what criterion was to be taken as to clubbing.

Professor Drummond referred to the frequency of clubbing of the fingers in certain hand workers, and Professor Meakins to the clubbing in polycythaemic children.

Several other members joined in the discussion.

The Annual Dinner was held in the Hall of Queen's College at 7.30 p.m. 132 members and guests were present. The President, Sir Archibald Garrod, was in the chair. The official guests were as follows: The Vice-Chancellor (L. R. Farnell, D.Litt.), the Mayor of Oxford (Mr. F. F. Vincent), Professor G. Dreyer, Professor J. A. Gunn, Mr. R. W. Chapman, Secretary to the Delegates of the University Press, and Rev. G. B. Cronshaw, Treasurer of the Radcliffe Infirmary.

OF GREAT BRITAIN AND IRELAND

SATURDAY, APRIL 22, 10 a.m.

1. Dr. A. Patrick related three cases of *non-diabetic glycosuria*. • These were cases in which sugar appeared in the urine, although the level of the blood-sugar was not above the renal threshold. He regarded such cases as comparatively common, and considered that they did badly if put on diabetic treatment.

2. Dr. George Graham discussed the *variations in the threshold in renal glycosuria*. He spoke of a new type of renal glycosuria in which sugar was excreted only after carbohydrates had been eaten. The threshold had been worked out in three cases, and in two of these sugar was not excreted until the blood-sugar was above 0.12 gm. per cent., and in one case 0.17 gm. per cent. The cases at first sight resemble mild cases of diabetes mellitus, but the diagnosis can be made by estimating the blood-sugar curve.

Dr. Spriggs advocated great caution in arriving at a diagnosis in this class of case. He drew attention to the occurrence of sugar in the urine in cases of sepsis, and termed this condition *septic glycosuria*.

Dr. H. Carlill, Dr. Hobhouse, Dr. Caton, and Dr. Leyton also spoke.

Dr. Patrick in reply suggested that the glycosuria occurring in some septic conditions might be due to a temporary lowering of the threshold.

3. Dr. G. Evans gave the results of investigations of four cases of *arterio-sclerosis* in children suffering with chronic nephritis. One died of cerebral haemorrhage and three of uraemia. They had very high systolic and diastolic blood-pressures. The large vessels showed a medial hypertrophy and the kidneys a diffuse hyperplastic sclerosis. He regarded the changes as inflammatory in nature; an arteritis, and the cause of the arterio-sclerosis the same as the cause of the nephritis, whatever that might have been. The communication was further discussed by Dr. Sutherland, Dr. H. Campbell, and Professor Drummond.

4. Professor W. E. Dixon gave an account of experimental work on the *secretion of the pituitary gland* which he had recently conducted. He stated that it was easy to demonstrate that the cerebro-spinal fluid of the dog contained a substance in every way corresponding to the pituitary extract. Injection of pituitary extract into the blood at once causes an increase of this substance in the C.S. fluid. This increase is due to an increased activity of the gland, for if the pituitary gland be destroyed, there is no increase in the amount of pituitrin in the C.S. fluid, and if the extract be injected directly into the C.S. fluid it at once passes out into the blood. Ovarian extract, boiled and filtered, causes an immediate increase in the amount of pituitrin. Extracts of alimentary mucous membrane cause a slow and gradual increase in about one hour.

5. Dr. C. B. Ker discussed the *relationship of herpes and varicella*. He related many cases of varicella following herpes. Herpes following varicella appeared to be much rarer, though the two conditions might appear almost simultaneously.

Professor Byrom Bramwell asked whether any member had seen a second attack of herpes or of poliomyelitis.

Dr. James Taylor referred to two cases of double attacks of herpes zoster, and Dr. J. A. Nixon had seen similar cases.

Professor Hall, Drs. Patrick, Newton Pitt, Mantle, and Gardiner also spoke.

6. Dr. J. A. Nixon related his experience of the *Schick test and active immunization for diphtheria*. He regarded the method as very valuable provided due precautions were taken.

Dr. Ker asked whether the immunizing method was capable of producing a rapid protection, as was desirable in a ward infection.

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Professor Hijmans van den Bergh gave a practical demonstration of his method for determining the presence of *bile pigments in the blood*.

By the kind invitation of the Delegates the members of the Association were taken over the Clarendon Press and given a demonstration of printing and other processes.

FRIDAY AFTERNOON. 3 p.m.

1. Dr. Starling gave statistics of the frequency of *endocarditis lenta* at Norwich before, during, and after the war. He had met with no cases in sailors. This type of cardiac disease appeared to be very prevalent amongst those who had served in the war, and to be rare amongst civilians. Men of the finest physique who had been subjected to great strain appeared to be specially liable.

Dr. Stobie (introduced) discussed the frequency of *endocarditis lenta* in Oxford during the years 1910-21. 1912 and 1920 were the years of greatest frequency.

Dr. Carey Coombs discussed the conditions predisposing to *endocarditis lenta*. He stated that in his series most of the cases occurring before the war were females; the mitral valve was that most frequently affected, and in 100 per cent. there was a history of rheumatic fever. Whereas after the war, the cases in the series were all males; 40 per cent. had a history of rheumatic fever, 20 per cent. had a syphilitic history, and in 90 per cent. the aortic valve was the one affected.

2. Professor Cowan and Dr. J. K. Rennie (introduced) gave the results of investigations of the post-mortem records of 81 cases of *chronic valvular disease*. Of these 37 (or 45 per cent.) presented evidence of an acute *endocarditis* as well, whilst 44 (55 per cent.) showed no signs of an acute infection. They did not agree that acute *endocarditis* was more prevalent after than before the war.

Sir Thomas Horder pointed out that cases of *endocarditis lenta* may present a picture of renal rather than cardiac insufficiency.

Drs. Ellis, Poynton, Stacey Wilson, and others joined in the discussion.

3. Professor F. R. Fraser described a method for producing *rapid digitalis effects by oral administration* in urgent cases of heart disease. He showed with the aid of charts that the action of digitalis is very rapid when the drug is given in one large dose. Two to three drachms of the tincture produce a marked effect in a few hours. He regarded this method as safer than the administration of strophanthin intravenously in urgent cases.

Professor Meakins also advocated caution in the use of strophanthin intravenously.

Dr. Emmanuel and Dr. Sutherland also spoke.

4. Dr. F. V. Cotton gave a communication on *clubbed fingers as a sign of infection in structural disease of the heart*. He showed that clubbed fingers were most frequent in aortic disease, and especially so in cases which showed evidence of infection.

Professor Fraser asked what criterion was to be taken as to clubbing.

Professor Drummond referred to the frequency of clubbing of the fingers in certain hand workers, and Professor Meakins to the clubbing in polycythaemic children.

Several other members joined in the discussion.

The Annual Dinner was held in the Hall of Queen's College at 7.30 p.m. 132 members and guests were present. The President, Sir Archibald Garrod, was in the chair. The official guests were as follows: The Vice-Chancellor (L. R. Farnell, D.Litt.), the Mayor of Oxford (Mr. F. F. Vincent), Professor G. Dreyer, Professor J. A. Gunn, Mr. R. W. Chapman, Secretary to the Delegates of the University Press, and Rev. G. B. Cronshaw, Treasurer of the Radcliffe Infirmary.

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Dr. Nixon in reply stated that immunization did not result before five weeks, whereas after a prophylactic serum dosage it might result immediately.

7. Dr. J. R. Charles related *three cases of manganese poisoning*. The early symptoms were those of fatigue, followed by undue emotionalism. The face became immobile, resembling the Parkinsonian mask: the voice monotonous and slow. Later the limbs became stiff, the gait spastic. If the condition were recognized early and the patient taken from his work, recovery might follow. If not, he became permanently crippled. He contrasted these cases with those due to lenticular degeneration.

8. Professor R. B. Wild discussed the relative values of morphine and codeine as general anodynes compared with the value of opium and its preparations. From his personal experience he considered that the liquid extract of opium was the safest and gave the best results. It was not followed by deleterious action on the alimentary canal.

Dr. Campbell and Professor Cowan criticized his remarks.

2-3 p.m.

An interesting series of clinical cases was shown at the Radcliffe Infirmary.

SATURDAY AFTERNOON, 3 p.m.

1. Dr. A. F. Hurst and Dr. J. R. Bell (of Melbourne, introduced) gave the results of investigations of the gastric juice in *Addison's anaemia*. Achlorhydria preceded the usual manifestations of the disease and was present in 90 per cent. of the cases. Four per cent. of apparently normal people had achlorhydria. In subacute combined degeneration the blood picture was often non-characteristic of Addison's anaemia, though the lemon-yellow complexion and achlorhydria were always present. *Streptococcus longus* was found in the duodenum in all cases, both of Addison's anaemia and subacute combined degeneration. They advocated for treatment of such cases one and a half drachms of dilute hydrochloric acid in a large bulk of water as a beverage.

Dr. Hunter referred to the presence of atrophic change in the gastric mucous membrane. He considered the presence of glossitis the most significant sign of the disease.

Dr. Hinds Howell referred to cases of subacute combined sclerosis which did not exhibit either the blood picture or the post-mortem signs of Addison's anaemia.

Dr. Tidy discussed the experimental production of pernicious anaemia. Ricin injected over long periods would produce this condition. He regarded the changes in the tongue, stomach, spinal cord, and blood in cases of pernicious anaemia as due to one and the same toxin.

Dr. Hutchison agreed as to the frequency of complete achylia and the importance of this in diagnosis. He had not found much benefit by administration of acids.

Dr. Symonds and Dr. Spriggs also spoke.

Dr. Hurst, in replying, said he did not believe that the achylia was necessarily due to atrophy of the mucous membrane, as atrophy might be absent. He could offer no explanations as to the cause of the achylia.

2. Dr. Payne and Dr. Poulton communicated the results of an *experimental investigation of dyspepsia*. A bag filled with water was passed into the stomach or duodenum and connected to a manometer. Contractions of the organ were registered by the manometer and could be charted. Painful sensations in the oesophagus, stomach, or duodenum investigated in this way seemed to be due to contractions in these organs. Counter-irritation, such as friction over the sternum, set up contractions in the oesophagus.

Dr. Hurst thought the pain was due to stretching of nerve fibres in the muscle.

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Dr. Poulton did not agree with this view, as he considered the pain was due to stretching of muscle fibres.

3. Dr. Hinds Howell pointed out our ignorance of the *pathogenesis of some cases of spastic paraplegia*. The type he referred to was one occurring in males about 56, without sensory changes or muscular wasting; usually progressive, but not tending to shorten life. Recently a P.M. examination on a similar case showed marked arterio-sclerotic changes.

Professor Kauffmann related two similar cases in middle-aged ladies.

4. Dr. Tyson related a case of *acute suffocative oedema of the lung* in a girl of 18. The onset was sudden, breathing became stertorous, T. — 101°. In a few hours she coughed up two pints of blood-stained frothy fluid. The signs in the lungs 12 hours after the onset were scattered moist sounds with slight dullness and bronchial breathing at the base of the left lung. He discussed the causation of such cases and considered that there were two types of the condition, one occurring in middle-aged women with heart and renal disease, and the second which appeared to resemble an abortive pneumonia.

Dr. Poynton referred to similar cases in children.

Dr. Parsons advocated atropine for treatment.

Dr. Ryle referred to the cases of phosgene gas poisoning during the war in which continuous oxygen administration was of the greatest value.

Drs. Young, Charles, Lewis Smith, Gardner, and Naish joined in the discussion.

5. Dr. Poynton, with Dr. Walsh and Dr. Greenfield (introduced), related a case of *progressive lenticular degeneration* in a girl of 16.

Dr. Walsh showed that the case filled a gap between the Kinnier Wilson type and the pseudo-sclerosis type of German authors.

Dr. Greenfield gave an account of the morbid anatomy of the case and showed photographs and specimens.

Dr. Gordon Holmes also spoke.



THE SEQUELAE OF EPIDEMIC ENCEPHALITIS IN CHILDHOOD, WITH NOTES ON THE PROGNOSIS AS REGARDS COMPLETE RECOVERY

By GRACE H. ANDERSON

(From the Medical Department, Royal Hospital for Sick Children, Glasgow)

Introduction.

SINCE the outbreak of epidemic encephalitis which began in Vienna in 1917 and appeared in this country in the spring of 1918, so much has been written on the subject that one hesitates to add to the already large and unwieldy bulk of literature.

It is not the purpose of this paper, however, to deal further with the disease from the point of view of aetiology and symptomatology, but to focus attention on the very distressing sequelae which have been brought to notice in the thirty-eight cases reported at this hospital. Eight of the cases occurred during the 1918-19 epidemic, nineteen during the 1919-20 epidemic (the majority occurring in spring 1920), and eleven occurred in the autumn of 1920 or the first two months of 1921. Twenty-three of the twenty-four cases formerly reported by Findlay and Shiskin (1) are included in this group.

On reading over the reports of the larger series of published cases, one is left in some doubt as to what are to be regarded as actual manifestations of the disease itself, and what are to be looked upon as sequelae. Much has been said recently regarding the possibility of the virus of the infective process remaining dormant in the nervous system and manifesting its undestroyed virulence by the production of periodic relapses.

Economo (2) observed one case during a period of two years, in the course of which several relapses were noted, and at the autopsy after the fatal termination he was able to demonstrate in the brain active inflammatory lesions which corresponded with the terminal symptoms. More recently Ely (4) in America has also called attention to this tendency to recurrence, and has given a full history of a case in whom several undoubted relapses occurred within a period of seven months. Harvier and Levaditi (3) were able to produce in the rabbit lesions identical with those found in epidemic encephalitis by the inoculation of an emulsion of the mid-brain of a patient who died fully six months after the initial attack, thus showing the persistence of the *contagium vivum*.

Moreover, most writers have been agreed as to the seasonal incidence of epidemic encephalitis, and Roger (7) has observed cases which, after apparent

recovery, showed a seasonal periodic recrudescence of symptoms. Consequently many of the so-called sequelae may more correctly come to be regarded as the results of fresh foci of inflammation in the functioning parts of the brain, and not, as has been suggested, of cicatricial contraction of the original lesion, of a toxin produced late by the virus (5), or due to functional factors combined with the primary organic lesion (6). The occurrence of progressive degeneration round the original focus of inflammation is also a possibility worthy of serious consideration, though ultimate recovery is rather against it. Most investigators, in reporting the typical disturbance of sleep, which is one of the most troublesome complications, and to which we have directed special attention, are agreed that a latent period usually intervenes between apparent recovery from an acute attack and the development of this phenomenon. The same may be said with even greater accuracy of the various troublesome habits, the psychical disturbances, and the mental deterioration which ensue. In the present state of our knowledge, therefore, it seems legitimate to designate these disturbances as sequelae, but whether or not they are the result of renewed activity on the part of the infecting agent must remain for future decision.

It is not intended in this paper to take paralysis into consideration when dealing with the sequelae, although it is admitted that this symptom may persist long after recovery from the actual illness. It has been our experience that paralysis, when present, occurs invariably during the early or late stages of the acute or primary attack, and tends rather to remain stationary or to improve than to become worse, a fact which has also been noted by Bonhoeffer (8) in his series of cases. The occurrence of paralysis after complete recovery from an acute attack was unknown in the fourteen cases followed from the beginning, and, when noted in the other cases, had either definitely been present as an initial symptom, or had been entirely unobserved by the parents prior to admission. The evidence collected from this series of cases points, therefore, to paralysis, which has most frequently affected the cranial nerves, as being a manifestation of the early stages of the disease, and it is for this reason that its exclusion from the list of the sequelae has seemed justifiable. At the same time it may be of interest to record the fact that twenty-two of the cases in this series suffered from paralysis affecting the cranial nerves (diplopia, paralysis of accommodation, and facial paralysis), that in three of these twenty-two cases paralysis of one or more limbs was present in addition, and that of the twenty-two cases fifteen had completely recovered from their paralysis at the date of writing, i. e. from two to four years after the onset of the illness. The most common type of ocular paralysis has undoubtedly been paralysis of accommodation, and this defect frequently persists for a long period even after accompanying paralysis of other cranial nerves has completely disappeared. At the same time it must be admitted that transient diplopia is a symptom which may have been frequently overlooked in children who are unable to describe subjective symptoms.

It is much more difficult to decide whether the symptoms belonging to the

so-called 'excito-moteur syndrome' are to be regarded as early or late manifestations of the disease. Marie and Lévy (9), who have given a very complete description of this syndrome, stated that, while these 'excito-moteur' symptoms frequently occurred early or late in the acute stages, they might also develop weeks or even months after apparent recovery from the initial illness. Indeed, these investigators went so far as to regard the occurrence of the 'excito-moteur syndrome' in a hitherto apparently healthy individual as conclusive evidence of the previous existence of the disease. They were among the first to suggest the importance of recognizing the existence of the disease in an abortive form or 'forme fruste', and believed that such mild attacks of encephalitis frequently escaped detection. Their conclusions appear to have been largely drawn from the fact, demonstrated by them, that the occurrence of this syndrome invariably followed the recognized seasonal epidemics of encephalitis lethargica. Hofstadt (10), in his very interesting discussion of the late manifestations observed in a large series of cases, described the motor disturbances under the two headings 'Amyostatischer Symptomenkomplex' and 'Chorea-athetose'. His cases clearly point to both of these phenomena being late rather than early manifestations of the disease.

A careful examination of the case reports of our series, however, points to the facts, not only that chorea has been the only commonly encountered symptom of the 'excito-moteur' type, but that in almost every case it has been a very early manifestation of the disease. The following figures may be quoted in support of this statement: Of the forty-one cases of encephalitis epidemica seen at this hospital twenty-five in all showed symptoms of chorea at some stage of the disease. Cases in whom choreiform movements were noted only during periods of night-restlessness are not included in this number. In all except three of the twenty-five cases the chorea was either personally observed by members of the staff to have been an initial symptom, or was described by the parents of the child as having been one of the first-noted disturbances. Indeed, not a few of our cases, as pointed out by Findlay and Shiskin, were sent into hospital with a diagnosis of chorea attached to them by outside physicians, and were only proved to be cases of encephalitis when the typical night-restlessness and psychical changes developed later. While the evidence in our hands, however, has led us to look upon chorea as an early manifestation, we have certainly been struck with the fact that frequent recurrence of this symptom with intermittent periods of latency is the rule. Moreover, in the cases admitted for observation of the night-restlessness, choreiform movements were frequently noted during the periods of nocturnal excitability, though they had not been in evidence during the day, and had never been described by the parents.

This fact is well brought out in the typical case history which I propose to record at some length when discussing night-restlessness. It is therefore evident that chorea may, and frequently does, considerably complicate the other manifestations which we regard as sequelae, and certainly tends to recur as long as other after-effects of the disease remain in evidence.

In the recent literature much attention has been directed to Parkinsonism as a not infrequent sequel of lethargic encephalitis in children and adults. Before leaving the subject of motor disturbances mention may therefore be made of the fact that symptoms strongly suggesting paralysis agitans have been encountered in only one of the cases of our series.

This patient gave a history of having had encephalitis in May 1920, and thereafter suffered from nocturnal sleeplessness and excitability of severe type for two years. Just when improvement in his sleep was giving rise to the hope of recovery, Parkinsonian tremor developed and he has since shown signs of gradual mental deterioration. At the date of writing, tremor is marked specially in the legs and feet, the face has become expressionless, and the speech is hesitating and indistinct. All his movements are slow and deliberate, but rigidity and typical stooping attitude are not present, and I have been unable to demonstrate propulsion and retropulsion though the patient has been examined repeatedly.

In three or four cases I have noted the presence of a mask-like expression apart from any facial paralysis and without other signs of Parkinsonism. In one case the expressionless face was associated with a slightly stooping attitude and very slow speech, which, however, suggested the scanning type described in connexion with disseminated sclerosis rather than the rush of words preceded by a period of hesitancy which one associates with paralysis agitans.

It is to be remembered that many of these children have difficulty in keeping awake during examination, and for this reason I do not, in the absence of other symptoms, attach too much importance to the expressionless face as an indication of the possible development of Parkinsonism. In this connexion I have noticed that several children whose faces were mask-like during the day were observed to have a particularly bright and alert expression during the wakeful hours of the night. The slow scanning speech, occasionally observed during the day, has also been reported by parents to have become quite normal during periods of nocturnal excitability.

These observations are of interest in view of the fact that Economo (12) has recently pointed out that patients of his who were unable to do anything for themselves during the day showed a remarkable ability to move about and attend to their wants during the night. Hofstadt (13) has also called attention to the remarkable degree of activity observed in the late evening and throughout the night in patients who appeared to be helpless during the day.

Muscle spasms of the myoclonic type, so frequently described by French and Italian investigators, have not been a feature of any of our cases, and I have never seen a case of Fröhlich's syndrome which could definitely be ascribed to a previous illness of encephalitis lethargica type.

To return, then, to the common sequelae, we will discuss them in what is considered to be their order of importance.

I. *Nocturnal Wakefulness and Excitability.*

(a) *Symptomatology.* During 1920 a peculiar type of sleep-disturbance encountered in a number of children in Glasgow was recognized as being a result of encephalitis by Findlay and Shiskin (1), who, independently of the observations on a similar condition which were being made about the same time in Germany, Italy, and Switzerland (Rolleston), made a special study of the phenomenon and published the first record of a large series of cases to appear in the English literature.

Since then much has been written concerning this peculiar after-effect in all countries, and, from a study of the recent literature and the consideration of the cases personally observed, we have come to regard nocturnal sleeplessness and excitability, with or without diurnal lethargy, in a child as conclusive evidence of the previous existence of epidemic encephalitis. I am not aware of any other disease which, in a hitherto healthy child, is known to produce the peculiar and striking type of night-restlessness one has seen in this series of cases. Hofstadt (10) went even farther than this, and doubted whether a diagnosis of a previous attack of encephalitis was justifiable in the absence of nocturnal excitability or Agrypnie, as it was called in Germany.

Certainly in our series of forty cases twenty-six are reported to have developed this symptom, and of the remaining fourteen, seven died during the acute stage and must therefore be excluded from the list of those in whom development of nocturnal restlessness was a possibility. I have made a very careful study of the seven remaining cases who did not develop signs of sleep-disturbance, but am still of the opinion, despite Hofstadt's statement, that they suffered from encephalitis lethargica. Two of them were admitted in the typical lethargic state, four gave a history of lethargy lasting some weeks, and the seventh had typical attacks of periodic chorea with mask-like facies and developed later psychical disturbance.

A parent's description of the behaviour of these children at night once heard is not likely to be either forgotten or ignored, and the striking similarity between all the histories is well brought out in a study of this series of cases. Those who have had to deal with epidemic encephalitis in children will no doubt be familiar with the type of story given. As an example of the usual course of events, however, it may perhaps be permissible to record in some detail the history of one of our more striking cases.

Case History.

E. R., a boy aged 9 years, was brought to hospital on March 4, 1921, and the history given by the mother was as follows: Before the onset of the present illness he had been healthy and his physical and mental development had been apparently normal. Four months before admission he took an illness which was diagnosed as pneumonia, but careful inquiry elicited the fact that fever, 'spasms

of the hands like St. Vitus' dance', and intense drowsiness, necessitating him being wakened for food, &c., had been the main characteristics of the illness. He recovered slowly from this illness after about three weeks, but it left him very weak. One month after recovery he ceased to sleep during the night, and falling asleep in the early morning would remain sound asleep till the afternoon. His behaviour at night is described by the mother as having been 'terrible'. He tore the bed-clothes, picking the blankets and sheets into incredibly small pieces, jumped from one end of the bed to the other, pulled down the hangings, insisted on getting up to go out and play, climbed all over the furniture, and made so much noise that the neighbours complained and the landlord threatened to have them ejected from their house. It was always necessary for one parent to sit up and watch him during the night. During the day while he was awake he was garrulous, silly, and forward, but remained quite reliable to send for messages and remembered all instructions.

On admission, during the day he was drowsy and resented being wakened, but once roused could answer questions with intelligence rather above the average, and he seemed to have an excellent memory. There was paresis of the left side of the face, and some loss of power in both arms, with a tendency to spasticity of the legs, and on physical examination very marked hyperaesthesia of the limbs was present, a condition which has not been noted in any other case, but which suggests the polyneuritic syndrome described by other writers. During residence in hospital he was excessively badly behaved at night. He got out of bed repeatedly and climbed up the water-pipes in the ward. On being told to lie down he did so, but whenever he attempted to settle down violent choreiform movements commenced and he very soon jumped up and commenced moving about again. When asked why he was behaving so badly he replied that he wanted to go to sleep, and frequently wept because he was unable to do so. On some occasions his restlessness at night amounted almost to acute mania. He was pinned down by means of sheets, but managed to get out and run about the ward. Later a stout wire frame was placed over his bed at night. He crawled about inside this and made a considerable disturbance, but was unable to do harm about the ward. During the day he was drowsy till well on in the afternoon. He then wakened up and gradually became brighter and more and more excited as the evening went on. The patient remained in hospital till March 21, i. e. about three weeks, and the problem of what was to be done with him was a difficult one, since his home circumstances were poor, and constant watching at night was essential.

Finally, he was notified as a case of encephalitis, and admitted to one of the fever hospitals. No more was heard of the child till three months later, when his mother brought him back, saying she and the rest of the family, as well as the child, were quite worn out, and begging us to do something.

His behaviour at night was evidently still exactly as it had been in hospital, and he could not be kept awake during the day. The unfortunate boy had been dragged about in a sleeping condition by his mother, in the hope that if she kept him awake during the day he might sleep at night. He simply went to sleep on his feet, however, dropped down whenever he stopped walking, and had to be shaken awake again. On examination at this date he was restless and garrulous. He took an intelligent interest in his surroundings and the examination, but at times answered irrelevantly and was undoubtedly a bit simple.

Orientation was good and his memory was excellent. No paralysis or paresis was apparent at this time, but marked hyperaesthesia of the limbs was still present. He was again seen seven months later and was still in exactly the same condition, but if anything more garrulous than formerly, and irrelevancy in his answers to questions had become more marked; he seemed incapable of fixing his attention for more than a few minutes, but memory and orientation remained good.

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Five months still later, or nineteen months after the onset of the illness, the mother reported that he had become so uncontrollable at night that he had been admitted to Merryflats Hospital for observation pending transference to Hawkhead Asylum.

The more striking characteristics of the nocturnal wakefulness noted in this and other cases are:

1. In the early part of the night an apparent inability to find a comfortable position in which to settle down. I have watched patients repeatedly get up and shake the pillow, lie down again for a few seconds, then take all the blankets off, and even sometimes the draw-sheet, shake up the mattress or try to turn it over, and lie down again with the cover hopelessly mixed up on top of him. He would remain quiescent for a few seconds, then try lying with his head at the foot of the bed and his feet at the top, and a large majority of the blankets hanging over the framework of the cot or lying on the floor.

2. As the night advances he apparently resigns himself to wakefulness and shouts for his toys to play with, singing, whistling, or talking incessantly while endeavouring to amuse himself. These may satisfy him for a few minutes, but if left alone he invariably gets out of bed, runs about the floor, performs vigorous gymnastic exercises over and around the cot and any furniture within reach, or demands his clothes in order that he may go outside to play. Spitting on the floor, soiling the bed, and smearing faeces over any object which can be reached are often characteristics of this state of restless activity.

3. In some cases, and generally after midnight, a condition amounting almost to acute mania has been observed, as in the patient just described.

4. Finally, in the early morning, the patient becomes gradually quieter and falls into sleep, which is at first troubled and restless, but which by the time the day is beginning for healthy individuals has become abnormally sound.

No one who has heard a number of descriptions such as this and has proved their accuracy by personal observation can fail to expect that the physical condition of both the child and the parents must soon suffer from the prolonged strain. It is, therefore, surprising to find that even after prolonged sleep-disturbance a large majority of the patients look well nourished and healthy. However, most, if not all, of the cases are unable to attend school or to be of any use during the day, and the problem of what is to be done for them is matter for serious consideration.

(b) *Prognosis.* From our own experience up till the end of 1921 we were of opinion that the condition was a chronic one and the prognosis as regards ultimate recovery exceedingly bad. A search of the earlier literature for information regarding prognosis failed to reveal much definite expression of opinion. The investigators who published the earlier reports of large series of cases naturally confined themselves to a prognosis regarding the immediate issue to life, and had not then realized the existence of an abortive form of the disease capable of causing severe and prolonged after-effects. Later, when attention came to be directed to this form and its sequelae, discussion was confined more to the

form which the sequelae were likely to take than to their probable duration and ultimate effect. Thirty-three of McNalty's (14) 93 non-fatal cases had not completely recovered at the end of three months, and Parsons (15) made the statement that in many instances the later stages of the disease had been much prolonged and that residual symptoms were common. Bramwell (16) noted that a few of his patients suffered from general weakness, slow mental action, lack of concentration, &c., for a long time after the illness. Happ and Blackfan (17) called attention to insomnia as a fairly constant sequel of encephalitis in childhood and expressed the opinion, from the observation of six cases, that the disturbance was a very persistent one. In Pfaundler's (18) cases the insomnia apparently lasted for many weeks, since none of them had recovered or improved at the time when he demonstrated them at Munich. Janecke's (19) case had insomnia which persisted for six months, but gradually recovered on improvement in his general condition. Hofstadt (10), from observations on a large series, was of opinion that of all the sequelae of epidemic encephalitis Agrypnie was the most common and the first to develop. He was also of opinion that in the case of sleeplessness he was dealing with a condition capable of being slightly improved. Several of his cases, however, whom he had observed for about eleven months, did not appear to have recovered completely at the time when he wrote his discussion. Reh's (28) two cases suffered from sleeplessness and agitation at night for seven and eleven months respectively, but both recovered permanently during an attack of measles. Two cases reported by Fletcher (20) recovered in about eight months and three months respectively, though in the latter child grunting and blowing during sleep succeeded the night-restlessness and appears to have persisted for some time.

Rolleston (11), in making a comment on Fletcher's cases, refers to the previous literature on the subject, and states that the features common to all the cases hitherto described are the long duration of the nocturnal restlessness, its association with other manifestations of epidemic encephalitis, and the inefficacy of treatment. The course of events in our series of cases certainly appears to confirm all three of Rolleston's statements, and the duration of the night-restlessness in most of our cases has extended much beyond the weeks and months suggested by the authors previously quoted, as the following figures will serve to show:

Of the 26 children suffering from this sequel 1 case recovered completely after 4 months.

2 cases recovered normal sleep after about 4 months, but were left with slight mental impairment.

1 case recovered completely after 11 months.

2 showed no improvement at the end of a year, when one was admitted to Larbert Institute for Defective Children, and one was lost sight of.

3 showed no improvement at the end of 1 year and 3 months and have since not been traced.

2 had shown no change at the end of 1 year and 6 months.

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2 were considered to be unmanageable at night and sent to Larbert Institute after having suffered for 1 year and 9 months.

6 recovered after about two years.

6 are still suffering from nocturnal sleeplessness and acute restlessness 2 years and 3 months after the illness, and of these 6, 3 are considered to be unmanageable, and are in institutions for the care of mentally defective children.

1 child who had encephalitis during the 1918 epidemic still remains sleepless 4 years after the onset of the illness.

The results in our cases are therefore far from encouraging, and certainly justify the belief that the condition of nocturnal restlessness which follows encephalitis lethargica in children is undoubtedly a persistent and a grave one.

(c) *The influence of age, sex, &c., on the prognosis.* The case histories have been specially analysed with the object of finding out whether any factor can be shown to influence the severity or duration of sleep-disturbance. Paterson and Spence (21) concluded, on tabulating the results in their cases, that the after-effects in infants and young children were much more serious than in the older children, and that the duration and severity of the initial illness had a definite bearing on the persistence and course of the sequels.

1. *Age.* The age of the child in our series appears to have little influence on the rate of recovery, though of course it is an established fact that nocturnal excitability as a sequel of encephalitis lethargica is a phenomenon peculiar to childhood, and has not so far been very commonly encountered in adults. Children of over twelve years are not admitted to the Royal Hospital for Sick Children, Glasgow, and therefore did not come indoors for observation, but it is undoubtedly true that the patients approaching this age showed as great a tendency to develop and retain sleep-disturbance as the younger cases included in the series. The age of the cases reported here ranged from two months to fifteen years, but the great majority of them were between six and twelve years old. In connexion with the conclusions of Paterson and Spence it is interesting to record the fact that four of the six patients who died were just under or just over one year of age—that is to say, the mortality is higher in the younger children.

2. *Sex.* The sex of the patient, so far as can be ascertained from this analysis, would also appear to have little influence on either the severity or duration of sleep-disturbance. It is, however, to be pointed out that only thirteen of our forty patients were girls, and that the disease in our experience has therefore been of more common occurrence in boys. This is also the experience of Neal (22) in America, and Hofstadt (13) in Germany.

3. *Nature of onset.* Neither, so far as can be discovered from this limited number of cases, has the nature nor duration of the onset any bearing on the persistence or severity of this after-effect. It is perhaps of some interest to mention here that the development of sleep-disturbance as a sequel is by no means confined to those cases in whom lethargy had been a feature of the initial illness, and that absence of sleep-disturbance at the commencement of the disease is no indication that subsequent nocturnal wakefulness with diurnal lethargy is

unlikely to develop. Indeed the cases who took longest to recover showed very considerable variation in the symptoms which characterized the onset, and encephalitis of the so-called abortive type or 'forme fruste' is frequently followed by disturbance of sleep sequence as severe as that found in cases where a definite illness of some duration has been noted.

4. *Year of onset.* Of the seven cases whose initial illness could be traced to the 1918-19 epidemic, three developed sleep-disturbance. In two of the cases sleeplessness continued for a long period, but the remaining case recovered completely after three months. All the remaining cases of sleep-disturbance occurred after the 1919-20 epidemic, with the exception of one in whom the acute illness developed early in 1921. The figures in the two groups are hardly comparable, owing to the very great difference in the number of cases belonging to the different epidemics and also to the fact that four of the 1918-19 group died during the acute illness. One can therefore only say that severe and prolonged disturbance of sleep sequence was not unknown as a sequel to the 1918-19 epidemic, but that most of our cases were encountered during the following winter, i.e. 1919-20. One can, however, draw attention to the fact that the wakefulness at night which ensued in the three children belonging to the first group was unaccompanied by the extreme degree of choreiform restlessness observed so frequently in the children of the second group. In fact we, in conjunction with other investigators, have been much struck by the fact that chorea has appeared as an accompaniment of the disease only in those cases belonging to the 1920 epidemic and was entirely unnoted prior to this outbreak.

(d) *Treatment.* Having discussed the factors, which might be expected to influence the course of night-restlessness, the question naturally arises, 'Is there any treatment known to alleviate or cure the condition?'

That no one form of treatment has been found satisfactory is sufficiently indicated by the number and variety of the suggestions made. Most investigators appear to have found that the usual doses of the ordinary soporifics and sedatives have little effect either in producing sleep or allaying the extreme restlessness. It has been our experience that large doses of chloral or bromide do produce sleep on three or four consecutive nights, sometimes even longer, but that their effect soon wears off and the patient returns to his old habits.

Several mothers have been emphatic in stating that improvement, in most cases temporary, definitely followed a complete change of surroundings and companions. For example, one girl, who had suffered from extreme night-restlessness for about four months, definitely, and in this case permanently, recovered normal sleep sequence during a stay with an aunt in the country away from all her home surroundings. In this connexion we have several times noted the curious fact that children admitted on account of extreme nocturnal restlessness and wakefulness have shown no sign of this phenomenon during the first few nights of residence in hospital, and in a very few cases have slept normally until their return home, when all the disturbances of sleep quickly returned.

Such an improvement must undoubtedly be ascribed to the complete change

from the usual surroundings and mode of life, since we had no cause to doubt the mother's story of the return of symptoms at home, but all the cases we have observed have been merely temporarily benefited.

One child who was admitted to a convalescent home in the country was reported by the matron to have slept at night only on condition that he was put to bed alone in a thoroughly darkened room and had been kept as quiet as possible for some time before the hour for retiring. The same child slept well while staying with an aunt who had no family, but his unruly behaviour returned whenever he was brought home. It is not to be wondered at, therefore, that this same child presented all the characteristics of nocturnal excitability in their worst form from the moment he was admitted to hospital till the time he was dismissed, since he slept in a ward amongst other children, where absolute quiet at night was impossible.

It would seem, then, that in some cases temporary improvement may result from sending the patient away from his home and surroundings, and this fact is well worth remembering when dealing with a case where both patient and family are worn out with the prolonged strain of wakefulness at night. At the same time this procedure has frequently failed to induce even temporary return to normal sleep sequence, and this is particularly the case with those patients in whom an extreme degree of motor unrest accompanies the nocturnal wakefulness. The importance of quietness and freedom from exciting stimuli is indicated by the fact that several patients who were definitely sleeping better relapsed badly on occasions when mild excitement of any kind was indulged in.

Lust (23) has written an interesting account of a child of one year and eight months who had suffered from sleeplessness of the typical kind for more than a year. On several occasions sleep was induced in this patient by means of intramuscular injections of milk. Lust attributed the improvement to a rise in the temperature caused by the protein reaction, since sleep failed to occur in the absence of this temperature rise, and moreover he found that the child invariably awakened if the temperature fell below the normal level during the sleeping period.

The conclusions of this author are of very special interest in view of the fact that recovery from sleeplessness is reported to have occurred during febrile illness. For example, Reh's (28) two cases made apparently permanent recoveries during an attack of measles which was presumably accompanied by fever. One of our cases showed a striking absence of his usual nocturnal wakefulness during an attack of scarlet fever, as did another patient of whom Dr. Findlay has kindly given me a history during an attack of mumps. This latter case will be mentioned later when discussing psychical disturbances.

Moreover, Hofstadt and others have reported that they were able to induce sleep by means of hot baths and the application of hot packs, both of which measures we know can raise the temperature of the body.

Temporary improvement was noted in six of nine cases treated by means of hypodermic injections of sterile water or saline solution in this hospital. The possibility of a rise in temperature as a probable cause of the sleep induced in

these children had not been brought to our notice, but a study of the charts has failed to reveal any alteration in temperature which could be ascribed to the treatment, and I am not aware that a simple hypodermic of water has ever been known to cause fever. Most of the charts, however, record only morning and evening readings, since the patients were not looked upon as being acutely ill, and variations occurring in the intervals may therefore have been missed. It seems perfectly evident, however, that the morning temperature in these cases was not as a rule higher than the evening temperature, though it is undoubtedly in the morning that the children begin the sleep which ought normally to have occurred during the preceding night.

The hypodermics of sterile water or normal saline solution were administered because of the apparently psychological action which they produce. The procedure adopted was as follows: The patient was approached usually about 10 or 11 p.m. and asked why he was not asleep. In most cases the reply was that the child desired to sleep but could not. The hypodermic syringe was then produced and the patient told that the injection about to be given would send him off to sleep in a few minutes. The sterile water was immediately given subcutaneously, the patient settled down comfortably and left alone. In six cases out of the nine treated by this means sleep was induced within about 15 minutes of the administration of the hypodermic. In two of the cases the child slept only for a few hours and then wakened, but in the remainder of the cases sleep lasted throughout the night.

Frequently it was unnecessary to give the hypodermic every night, since sleep was often induced on one or two succeeding nights by merely telling the nurse in the hearing of the patient to have the instruments ready in case they should be needed. This fact strongly suggests that the fear of undergoing the pain of the injection is largely responsible for the good result, though in those cases where nightly repetition of the hypodermic was necessary we were more inclined to the belief that sleep was the result of the strong suggestion made to the patient beforehand that the treatment would be successful. This supposition was also supported by the fact that the treatment was much more successful in some hands than in others, and that it was a conspicuous failure in very young patients.

A striking example of the importance of suggesting unfailing success to the patient was afforded in one of the cases whom I personally treated.

R. C., a boy aged 7½ years, had suffered from night-restlessness and insomnia for over a year. He had been treated in hospital with soporifics, had been sent away twice to a convalescent home, and had been dragged about during the day in the hope that sleep at night would be the result, but without any improvement. Finally, at Dr. Findlay's suggestion, I arranged for him to be brought to hospital each night for a hypodermic of sterile water. The patient was brought each evening about 7 p.m., given the injection after being assured that sleep would result, and taken straight home to bed. It was found necessary to give the dose every night, although the boy was much afraid of the skin puncture, which appeared to cause considerable pain. This was continued for a fortnight, during which the patient went to sleep regularly between 10 and 11 and slept till morn-

ing. Home circumstances after this prevented the mother from bringing the child to hospital, which was a considerable distance away from her district, but the situation was explained to their family physician, who agreed to carry out the treatment at home. Unfortunately the child overheard a conversation during which it was explained to the mother that the treatment was given for its psychological effect and that the dose itself had no sleep-producing properties. Thereafter the treatment ceased to have any effect, either in the hands of the outside doctor or as carried out by myself when the child was brought back to hospital.

In no case have we been able to carry out a course of hypodermic injections over a prolonged period, and are not, therefore, able to say whether any permanent result might be obtained by means of making the child believe that the dose was being gradually decreased and would finally prove unnecessary. Certainly, however, if the child is sufficiently old to be a suitable subject for suggestion, the treatment would be well worth trying. Findlay and Shiskin (1) have mentioned how hypnotism was tried in one or two cases, but without much success, the patients being apparently too young. We have not been able to try the effect of hypnotism on any of the older patients.

II. *Psychical Disturbances.*

(A) CHANGES IN DISPOSITION. Kirby and Davis (24) have stated, after making a study of lethargic encephalitis, that some change in disposition nearly always remains and may be the only sign of incomplete recovery. An analysis of our cases has amply justified the statement of these investigators.

Hohman (25) has recently given a detailed description of the various psychical manifestations encountered by him in a series of 23 cases in adults, and has classified them in a very interesting paper. These changes amongst our patients have been so involved and so frequently complicated one with the other that a detailed description of them must of necessity prove difficult to any but experienced psychologists.

Certain phenomena do, however, stand out clearly from amongst the tangle of emotional and psychical changes, and for the purposes of general description are grouped here under the heading of changes in disposition.

The type of history given by the relatives is usually very similar to the following one, which I quote from a case report:

J. McF., aged 7 years, suffered from an illness characterized by extreme lethargy, choreiform movements, ocular paralysis, and neuralgic pains in the limbs, early in June of 1920. He was admitted to hospital at that time, and was considered to be undoubtedly suffering from lethargic encephalitis. All symptoms gradually cleared up, and the patient, except for inequality of the pupils, had apparently recovered by July 13, 1920. On August 11 of the same year he was brought back to hospital complaining of nocturnal insomnia of the typical kind. This disturbance has continued up till the present, i.e. two years after onset, but is now showing signs of improving.

When seen in May of this year (1922) the mother complained that the patient's 'disposition had altered so completely' that she could hardly recognize

him as her own child. He had become excessively disobedient and frequently suffered from violent fits of temper which were quite unprovoked. Emotional disturbance was present in the form of bouts of miserable weeping followed by uproarious laughter, singing, and whistling. He was cruel to his brothers and sisters and to his playmates, and the parents had received several complaints about his habit of kicking animals in the streets. His destructiveness was a source of much worry and expense, since he seemed to delight in putting his 'fist' through a window, in defacing the furniture, or in breaking the china. More recently he had been found stealing things from home and from shops, and lying cleverly about them when questioned.

The condition of this patient to-day is such that he requires to be constantly watched, and the psychical disturbances described by the mother are so much worse at the moment that I fear confinement in some institution may prove necessary.

Disturbances similar to this, though not always as severe, have occurred in as many as twenty-five of our patients. Seven of this number showed disturbances of psychical type only during the period of nocturnal wakefulness and were so drowsy during the day that no abnormality was noticeable.

In all of the remaining eighteen cases except one the diurnal psychical disturbance was accompanied or had been preceded by nocturnal wakefulness and excitability, and in most cases the latter sequel had been in existence for some time before the former disturbances were noted. These figures confirm the statements of Hofstadt (10), Paterson and Spence (21); and others, that the two conditions are very frequently associated.

It will be seen from the case report just quoted that the characteristics standing out most clearly from the symptom complex of dispositional changes which go to make up the naughty child are: (1) disobedience; (2) irritability and unprovoked fits of temper; (3) cruelty to relatives and to animals; (4) destructiveness; (5) emotionalism; (6) kleptomania.

On examining all the cases whom it has been possible to trace at a recent date it is found that disobedience, irritability, and fits of temper have developed in thirteen cases; garrulity, described by Hohman (25) as 'a great push of talk without distortion of stream of talk and without mood alteration', also in thirteen cases; destructiveness in seven cases, and cruelty in seven cases; while a disturbance resembling kleptomania, and accompanied always by lying and deceitfulness, has been encountered in five of the cases. Only two of the children became phenomenally emotional.

Garrulity was frequently present as the sole psychical disturbance, but disobedience, irritability, and bad temper were always associated with other physical disturbances, and destructiveness and cruelty seldom occurred apart from each other, the impulses to injure inanimate objects and people being apparently closely associated.

(a) *Effect of changes in disposition on the mental standard.* In examining patients brought to hospital on account of psychical disturbances there are several points about the condition of the children which strike one very forcibly.

The first of these is that, after having seen and conversed with a large

number of the so-called naughty children, one is left with the general impression that their intelligence has suffered surprisingly little impairment considering the amount of psychical disturbance which is present. In other words, one would look upon them as moral rather than mental imbeciles. Our own impression was borne out by the very frequently repeated statement of the mothers that the children remained clever and intelligent 'if they would only behave better'. This idea of the mental standard was, however, merely gathered from answers received to general questions put during ordinary examination, and it was obvious that more skilled investigation was necessary. We were, therefore, fortunate in obtaining the co-operation of Dr. Watt, Lecturer on Psychology, Glasgow University, who kindly examined a number of our patients with a view to testing their standard of intelligence.

His results so far have failed to confirm our first impression, since the mental ratio of the five children so far examined has been between 70 and 80, that is to say, they have all been on the borderland of mental defect. In only one case have I known complete imbecility to develop as a sequel of encephalitis, and this was in a child who suffered from the disease at the age of 13 months. The initial illness lasted about four weeks. One month afterwards he suffered from night-restlessness, and thereafter gradually became more and more dull and helpless till at the age of 2 years and 9 months he was unable to sit up or to recognize his parents. He died from broncho-pneumonia while in this helpless condition.

Ten other children, at the date of writing, suffer from mental defect which is easily discoverable on ordinary routine examination, but, strangely enough, they fail to show the psychical disturbances characteristic of the badly behaved group. In fact, it has been our experience that the moral imbeciles do not suffer from severe mental defect, and conversely that those suffering from severely impaired intelligence do not present psychical and emotional disturbances in any marked degree.

Paterson and Spence (21) have called attention to the medico-legal importance of this moral defect when reporting the interesting case of a boy who had on several occasions been convicted of theft, though prior to his attack of epidemic encephalitis he had been a well-behaved normal child. In the experience of these two investigators mental defect seems to have been of much more common occurrence than moral perversion. Of their three cases described as suffering from marked change of disposition, however, only one appears to have been mentally backward. In consequence of their medico-legal interest these points seem worthy of further investigation.

The second noteworthy characteristic of these morally defective patients is the fact that they have all excellent memories, and I must admit that this may play a considerable part in giving one the impression that their intelligence is not markedly impaired. Hohman has also called attention to the remarkably clear memory of many of the adult patients under his care who were suffering from disturbances following encephalitis lethargica.

The third and last point which seems to deserve mention in connexion with

the naughty child is his ability to realize the fact that he is behaving badly. The child whose history is given in full frequently stopped in the middle of a bout of fierce temper and destructiveness, and after a few minutes' thoughtfulness would remark in a sad tone, 'I am a very bad boy, I know I am a bad boy, but I cannot help it.' Several others amongst this series of patients have had the same type of remark ascribed to them by the nurses and parents. They appear to be acutely conscious of the impulse to do wrong, but are quite unable to explain or control it.

(b) *Prognosis.* Only one of the children reported to have developed psychical disturbances has completely recovered, but several, after periods varying between 18 months and $2\frac{1}{2}$ years, are beginning to show decided improvement in their behaviour.

(c) *Influence of age, sex, &c., on psychical disturbances.* 1. *Age.* With regard to the influence of the patient's age on the nature or persistence of the ensuing psychical disturbances, it would seem from our cases that the younger children tend to suffer mental impairment rather than moral perversion, and that the older children show a tendency in the opposite direction. Owing to the failure of the cases to recover up to the time of writing, I am not able to say whether age has any influence on the rate of recovery.

2. *Sex.* Boys and girls appeared to be affected in this way with equal frequency and severity.

3. *Nature of onset.* I am not able to demonstrate any connexion between the nature or duration of the onset and the type or severity of the psychical phenomena.

4. *Year of onset.* All of the three children who survived the 1918-19 epidemic showed varying degrees of mental impairment without any noticeable change in disposition. Most of the typical cases of psychical disturbances have therefore been encountered as a result of the 1919-20 epidemic.

(d) *Treatment.* I am not familiar with any treatment which is known to accelerate recovery. It is, however, significant that those patients who have been sent to institutions have undoubtedly shown more improvement than the cases not so treated, and that the earlier they are admitted to homes where skilled attention can be paid to their psychical state the better the results are likely to be.

(B) *HABITS.* The post-encephalitic disturbances which we describe as habits might perhaps be included in the group of psychical sequels. We give them a separate description, however, in the first place because the parents have usually described them in addition to, and apart from, changes in disposition, and in the second place because they differ from the other psychical symptoms in that the patient can control them when checked.

(a) *Spitting.* By far the most common and the most distressing of the unfortunate habits encountered in children who have suffered from encephalitis is spitting. Netter (26) described and laid considerable stress on sialorrhoea as one of the symptoms of the acute illness. This increased salivation appears to have

been a marked feature of many of his cases, so much so that Netter believed that the virus was present in the saliva, and even suggested that elimination of the infective organism could be hastened by giving drugs like pilocarpin.

We have not encountered sialorrhoea during the acute stage of the disease in any of our cases, but the spitting habit developing as a sequel has been in most cases sufficiently severe to justify us in considering the possibility of its being due to excessive secretion of saliva. This supposition also gains further support from the fact that the thirst resulting from the loss of fluid caused by the habit has, in many cases, been sufficiently excessive to cause the parents to suspect that the patient was suffering from 'drinking diabetes'. The naughty children have frequently very voracious appetites, and I am inclined to think that the thirst is merely an accompaniment of this. Moreover, the fact that the patients show a marked tendency to spit at their companions and on objects which they know are valued by others seems to indicate that the spitting habit is part of the psychical disturbance, and also, as already indicated, the patients are able to control the habit of spitting quite successfully when checked for it, and are able to refrain from it for long periods if watched. One child suffering from this disturbance was known in her own district as 'Spitting Jean', and was so tormented by all the children in the neighbourhood that her life was very miserable. Yet the child, if told not to spit and kept under supervision, could easily control the habit for a considerable time without any apparent accumulation of saliva.

Spitting and other dirty habits, such as defaecating on the floor or urinating on the walls or on the cots of other children, have also been a frequent accompaniment of the night-restlessness in hitherto cleanly children, which habits have persisted as long as the sleep-disturbance lasted.

(b) *Hyperpnoeic breathing*. The second disturbance to be described amongst the habits is the so-called hysterical or hyperpnoeic breathing. This has been present in all the children showing severe psychical disturbances and varies very much in type. The phenomenon is apparently not found exclusively in childhood, since a similar disturbance has been noted by others in adults. One case described by Barker and Sprunt (27) suffered so markedly from this type of breathing that on one occasion hyperpnoeic tetany resulted.

In some of the cases the breathing was very rapid, resembling that seen in cases of pneumonia, but differing from it in that it was noisy. The parents frequently described children suffering from this type as having bouts of 'panting like a dog', and this is perhaps as good a description of the phenomenon as can be given. In others, the breathing is very slow and noisy with prolonged expiration, all the muscles of forced respiration being brought into action.

It is somewhat difficult to find out whether this hysterical dyspnoea is the result of some exciting stimulus. There is no doubt whatever about the fact that the attacks are paroxysmal, but I have not been able to demonstrate any constancy in the time interval between each paroxysm. Patients are very frequently breathing in the hysterical fashion when brought into the room for examination,

and immediately stop it when the attention is directed towards the general examination. It has also been noted that children lying in the wards behind a screen, and apparently quite quiet and contented, suddenly commence an attack of this kind, which can be immediately arrested by clapping the hands or by merely walking round the screen and speaking to the patient. It would therefore seem that the patient is able to control the impulse to hyperpnoeic breathing when he is made aware of it. On the other hand, I have seen children beginning to breathe in the typical fashion apparently as a direct result of some exciting stimulus, and these patients are unable to control the disturbance until they have been removed from the cause of excitement.

The hyperpnoeic breathing habit occurs in most cases soon after recovery from the initial illness, and none of the children who developed the sequel has recovered or improved at the time of writing, though the frequency with which the paroxysms occur is subject to marked fluctuation.

(c) *Other habits.* In isolated cases other habits such as eye blinking, head rolling, and stammering have been encountered, but are not of sufficiently frequent occurrence to deserve special mention.

One child was brought back to hospital with the complaint that since his illness he had developed a striking peculiarity in his gait, which was described as follows: While walking along quite normally he would suddenly stop, bring his feet together sharply, jump into the air, and run a few steps, then resume the normal gait once more. The child was admitted to hospital for observation, but though kept in for ten days failed to show any sign of the peculiarity described. On his return home the habit returned, and was apparently of sufficient frequency to occasion much comment from people who saw him in the street.

Another patient, of whom Dr. Findlay has kindly permitted me to give this description, developed the very peculiar habit of stopping suddenly in her play, taking a long forced inspiration, holding her breath, and then, with hands clenched and lips firmly closed, straining forcibly as if trying to defaecate. The straining was so forcible and so frequent that all the veins of the scalp were distended and the skull grooved under them, and the muscles of the chest and back so strikingly over-developed that the patient, a female aged 3 years, looked like a miniature prize-fighter.

(d) *Prognosis.* I am not able to record marked improvement in any of the children who have developed unfortunate habits up till the time of writing, though some of them have been suffering from such sequelae for periods of over two years.

(e) *Treatment.* The fact that Dr. Findlay's patient was free from symptoms during a febrile attack suggests the possibility that the protein reaction fever Lust (23) produced with temporary benefit in sleep-disturbance might also cause temporary cessation of habit peculiarities. Careful training and correction would seem to be the only remedies giving any hope of permanent benefit.

III. *Summary and Conclusions.*

From a study of forty cases of encephalitis lethargica in childhood we have come to regard disturbance of sleep sequence, psychical changes, and the development of troublesome habits as the most frequent sequelae.

Chorea, when present, almost invariably developed during the acute or primary stage of the disease, but tended to recur in combination with the various sequelae for long periods after apparent recovery. Other forms of motor unrest were not encountered in this series of cases and no instance of the myoclonic type of spasm was observed.

Paralysis of cranial nerves was not uncommon during the acute illness, but never recurred, and in all the cases tended either to improve or remain stationary.

Typical Parkinsonian tremor developed in only one case, but a mask-like expression, in some cases accompanied by slow scanning speech, without other symptoms of paralysis agitans, was of frequent occurrence.

Disturbance of sleep sequence occurred in twenty-six of the thirty-three non-fatal cases, and persisted for periods of from four months to four years. The large majority of the children suffered from the disturbance for at least two years, and in many instances were the subjects of psychical changes or mental impairment at the end of that time. The prognosis is therefore bad. We have not been able to conclude that either age, sex, year of onset, or severity and duration of the initial illness have any effect on the severity or duration of this after-effect.

Treatment is unsatisfactory, the usual soporifics in ordinary doses having little effect on the condition. Temporary benefit has been obtained by complete change of surroundings and quiet, by hypodermic injections of milk which cause a rise in temperature, and by subcutaneous injections of sterile water.

Psychical disturbances developed in twenty-five of the patients, and consisted usually in a complete change of disposition, of which the main characteristics were disobedience, excessive irritability, and unprovoked fits of temper, cruelty to relatives and to animals, destructiveness, emotionalism, and, more rarely, kleptomania. The change in disposition was, in our experience, seldom accompanied by any marked degree of mental impairment.

Definite mental impairment ensued in ten of the children, all of whom showed a striking freedom from the psychical disturbances characteristic of the badly-behaved group.

Only one child has recovered from the psychical change at the time of writing, but several who have been admitted to institutions are beginning to show signs of improvement after two years.

As in the case of sleep-disturbance, no connexion can be demonstrated between the sex, the year of onset, or the severity of the initial illness, and the severity or duration of the psychical changes. It would seem from our cases, however, that the younger children show a greater tendency to become mentally impaired and the older children to develop changes in disposition.

The only treatment which appears to have had any effect on the condition is careful training and supervision in an institution for defective children.

Of the troublesome habits which developed as a result of encephalitis lethargica, spitting and hysterical or hyperpnoeic breathing were undoubtedly the most frequently encountered. Other habits of a more or less distressing nature have been observed, but not with sufficient frequency to deserve special attention.

None of the children suffering from habit peculiarities has recovered, though some have been under observation for over two years, and no treatment is known to affect the condition.

Before concluding, I wish to take the opportunity of thanking Dr. Leonard Findlay for his permission to make this further study of his cases and for his helpful criticism of my paper.

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THE CHOLESTEROL CONTENT OF THE BLOOD IN ANAEMIA, AND ITS RELATION TO SPLENIC FUNCTION

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Introduction.

CONSIDERABLE attention has been devoted in recent years to the lipoids of the blood, and to the part they probably play in various normal and pathological processes in the animal economy. Of the substances included in this class, cholesterol and its esters appear to be the most important. Much has been written about its relation to immunity and to the production of antibodies. Cases of bacterial infection are almost invariably accompanied by a marked hypocholesterolaemia, while the low content, and often complete absence, of lipoids in the cortex of the suprarenals in subjects dead of infective conditions is now well recognized.

A striking increase in the cholesterol content of the blood has been noted in many diverse conditions, e.g. arterio-sclerosis, chronic nephritis, obstructive jaundice, cholelithiasis at certain times, and the later stages of pregnancy. In addition, its relation to fat metabolism is shown by the marked hypercholesterolaemia invariably associated with the lipaemia of severe diabetes.

The rôle of cholesterol in haemolysis has also been the subject of much experimental investigation. It has been shown to act as an antihæmolytic agent against such substances as saponin, tetanolysin, and cobra-venom; on the other hand, the phosphatide lecithin acts antagonistically in this respect, for it activates the lysin. On the clinical side, Bloor (1) has reported the presence of a low cholesterol content of the blood in a series of cases of anaemia, especially when severe in type.

The spleen is generally regarded as the organ in which the red blood-cells are destroyed. Considerable additions to our knowledge of this subject have resulted from the important work of Pearce (2) and his collaborators on the relation of the spleen to blood destruction and regeneration. This has led to some observations on the effects of splenectomy on the cholesterol content of the blood. King (3) has found, after removal of the spleen in dogs, an increase in the fat and cholesterol of the blood, while in a splenectomized animal poisoned with toluyldiamin the increase was exceedingly striking.

[Q. J. M., April, 1923.]

A few records have been made by Bloor (1) of the cholesterol findings after splenectomy in anaemic conditions. In four such cases (the type of anaemia not being recorded) a slight increase in cholesterol is noted after splenectomy. Only one post-operative estimation was carried out, however, and no reference is made to the length of time elapsing between the operation and the cholesterol estimation. This is a point of some importance, for we have noted, in the course of investigating the blood cholesterol in other conditions, that a decrease for a longer or shorter time invariably follows any major operative procedure. In view of our findings, probably a much more striking increase would have been found if the variations in cholesterol had been followed up for some months after splenectomy.

Through the courtesy of Sir Berkeley Moynihan, we have been able to follow up, for a period of three months or longer, the changes in the cholesterol content of the blood after splenectomy in three cases of haemolytic jaundice and one of splenic anaemia, while we have attempted to correlate any variation in the fragility of the red corpuscles, &c., in these conditions. At the same time we have carried out an investigation on the total cholesterol of both plasma and red corpuscles in a series of twenty-five cases of diseases of the blood, all of them different types of anaemia, except two cases of polycythaemia vera. The following is a list of our cases: secondary anaemia, 6; pernicious anaemia, 6; myeloid leukaemia, 4; lymphatic leukaemia, 1; splenic anaemia, 2; familial acholuric jaundice, 4; polycythaemia vera, 2.

Method employed in the Estimation of Cholesterol.

The estimation of the total cholesterol of the blood, both of plasma and corpuscles, has been carried out by Myers and Wardell's (4) method, slightly modified. With this technique, cholesterol can be recovered quantitatively; consistent duplicates can be obtained, and the findings are in satisfactory agreement with those obtained by the standard gravimetric method of Windaus. The method, which is comparatively simple, is a colorimetric adaptation of the Liebermann-Burchard reaction, the cholesterol being first extracted from the dried blood-plasma with chloroform as the solvent.

The following is a detailed account of the method as found most reliable and satisfactory by us:

1 c.c. of the blood-plasma or serum is pipetted into a porcelain crucible containing from 4 to 5 gm. of plaster of Paris, is stirred, and then dried in a drying oven for $\frac{3}{4}$ hour at 70–80° C. The dried powder is then carefully emptied into a small fat-extraction capsule (5 × 2 c.m.), which is inserted into a short glass tube (6 × 2.5 c.m.) in the bottom and sides of which are a number of small perforations. This tube is attached to a large cork through which passes the end of a small reflux condenser, and the tube and cork are inserted into the neck of a 150 c.c. flask, containing about 25 c.c. pure chloroform. Extraction is continued for one hour, at least, on an electric hot plate. The chloroform solution

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is then made up to 20 c.c., filtered if necessary, and the colorimetric estimation is carried out as follows :

5 c.c. of the chloroform extract are pipetted into a dry test-tube ; then 2 c.c. of acetic anhydride and 0.1 c.c. concentrated sulphuric acid are added. After thorough mixing, the solution is placed in the dark for fifteen minutes (preferably at 22° C.) to allow the colour to develop. It is then compared in a Kober colorimeter with a standard cholesterol solution in chloroform (0.4 mg. cholesterol in 5 c.c. chloroform) which has been similarly treated with acetic anhydride and sulphuric acid.

The procedure for the estimation of cholesterol in the red blood corpuscles is exactly similar, the corpuscles having first been freed from plasma by three successive washings with normal saline solution, and subsequent centrifugalization.

As to the modifications introduced by us into the original technique, we found it more reliable to allow the extraction to continue for one hour, as it was incomplete at the end of thirty minutes as recommended by Myers and Wardell. In the drying process, also, great care has to be exercised to prevent overheating, the most suitable temperature having been found to be 70–80° C. If this be exceeded the plaster of Paris assumes a brownish colour, and the dried blood-plasma, after chloroform extraction, gives a very weak colour reaction as compared with that obtained when overheating has been avoided.

Myers and Wardell recommend an aqueous solution of naphthol green B as standard, but the colours are more evenly matched when a solution of pure cholesterol in chloroform (0.4 mg. cholesterol per 5 c.c.) is used.

The optimum temperature for the development of the colour reaction was found to be 22° C., as pointed out by Bloor. He showed that the blood cholesterol behaves differently from the standard cholesterol. The former acts more readily with the reagents, reaches its maximum depth of colour sooner, and begins to fade more quickly than the standard solution of pure cholesterol. The rate of development of colour in the two solutions is more uniform at 22° C. than at higher or lower temperatures.

Our experience agrees with that of Myers and Wardell as to the absolute necessity of using perfectly anhydrous reagents in order to avoid weak colour reactions. This has to be borne in mind in making use of chloroform recovered by distillation from old extractions.

The Cholesterol Content in Pathological Conditions of the Blood.

Using this method of Myers and Wardell, we found the normal cholesterol content of the blood-plasma in a series of twelve normal cases to vary between 0.191 per cent. and 0.133 per cent. with an average of 0.161 per cent. These values are in agreement with those of other workers, e.g. Chauffard, Laroche, and Grigaut (5), whose figures range between 0.180 and 0.150 per cent.

We have recorded in Table I the total cholesterol of the blood-plasma, and in many instances also of the red corpuscles, in the twenty-five cases of anaemia,

TABLE I. *Cases of Secondary and Idiopathic Anaemia, &c.*

No.	Initials.	Age.	Sex.	Disease.	Cholesterol (grm. per 100 c.c.)		Blood-count.			
					Plasma.	Corpuscles.	Red cells.	Hb %.	Colour Index.	Leucocytes
1	A. S.	53	M.	Normal health	0.162	0.110	3,400,000	45	0.7	4,800
2	J. H.	5	M.	Secondary anaemia following haematemesis	0.157	—	3,900,000	40	0.5	6,000
3	J. B.	45	M.	Secondary anaemia	0.120	0.082	2,800,000	50	0.9	3,800
4	A. S.	33	F.	Secondary anaemia following metrorrhagia	0.090	—	2,000,000	25	0.6	4,200
5	E. T.	35	F.	Secondary anaemia (following post-partum haemorrhage)	0.103	0.119	980,000	18	0.9	3,300
6	A. M.	49	F.	2nd exam. (4 months later)	0.122	—	4,800,000	75	0.7	6,600
7	A. W.	34	F.	Secondary anaemia (syphilitic)	0.175	—	3,900,000	35	0.5	2,300
8	A. M.	30	F.	Pernicious anaemia	0.107	0.070	1,800,000	35	1.0	2,600
9	A. F.	38	F.	2nd exam. (3 months later)	0.090	—	1,000,000	20	1.0	3,600
10	H. H.	48	M.	Pernicious anaemia	0.070	—	800,000	15	0.9	2,800
11	J. G.	54	M.	Pernicious anaemia	0.140	0.080	2,400,000	50	1.0	5,600
12	E. P.	33	M.	Pernicious anaemia	0.132	0.117	2,700,000	55	1.1	6,400
13	E. W.	35	F.	Pernicious anaemia	0.072	—	900,000	20	1.1	3,000
14	J. B.	57	M.	2nd exam. (3 weeks later)	0.131	0.081	2,200,000	40	1.0	6,500
15	T. W.	55	M.	Myeloid leukaemia	0.110	0.077	3,400,000	68	1.1	5,200
16	W. A.	56	M.	Myeloid leukaemia	0.104	—	3,200,000	40	0.6	210,000
17	W. J.	67	M.	Lymphatic leukaemia	0.127	—	5,100,000	70	0.7	220,000
18	H. C.	20	M.	Acholaric jaundice	0.109	—	5,000,000	60	0.6	10,000
19	N. B.	28	F.	Acholaric jaundice	0.099	—	4,500,000	55	0.6	280,000
20	J. W.	60	M.	Acholaric jaundice	0.090	—	4,000,000	45	0.6	110,000
21	S. G.	28	F.	Acholaric jaundice	0.108	—	2,800,000	20	0.4	900,000
22	S. P.	37	M.	Banti's disease	0.060	—	4,250,000	70	0.8	5,600
23	W. M.	14	M.	Banti's disease	0.094	—	2,600,000	40	0.8	3,800
24	R. R.	55	M.	Polycythaemia vera	0.097	0.077	3,000,000	40	0.6	6,400
25	W. M.	30	F.	2nd exam. (1 week later)	0.112	0.105	3,700,000	45	0.6	1,700
				Polycythaemia vera	0.121	—	6,200,000	85	0.7	10,200
				2nd exam. (3 weeks later)	0.087	0.107	9,500,000	115	0.6	21,200
					0.074	0.121	7,700,000	115	0.7	9,800
					0.076	—				
					0.190	—				
					0.185	—				

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&c. It will be noted that in most cases the cholesterol content of the plasma is diminished, although the decrease is not striking until, as pointed out by Bloor, the red cell count is less than 50 per cent. of the normal. The only high value obtained in the series (viz. 0.175 grm. per 100 c.c.) was in the case of a woman aged 49, suffering from anaemia of syphilitic origin, and it is interesting to note that she showed definite signs of arterio-sclerosis.

No noteworthy difference in the blood cholesterol in cases of secondary and of pernicious anaemia is seen. Both conditions give low values when the anaemia is profound; nor in milder cases is there any correlation between the total cholesterol content and the colour index.

The findings in the two cases of polycythaemia vera are equivocal. In the one case, an elderly man aged 55 who had a count of 9,500,000 red cells, cholesterol = 0.074 per cent., while in the other, a woman aged 30, the cholesterol content = 0.190 per cent. with a blood-count of 7,700,000. A boy aged 14, suffering from Banti's disease, with a red cell count of 6,200,000, had the low cholesterol value of 0.087.

The leucocytes appear in no way correlated to variations in the plasma cholesterol. Thus in a case of myeloid leukaemia the leucocyte count fell within eight weeks under X-ray treatment from 220,000 to 10,000, the corresponding cholesterol values being 0.127 and 0.109, while there was little difference in the red cell counts, viz. 5,100,000 and 5,000,000.

In the various grades of anaemia, some decrease in the cholesterol of the red corpuscles is to be noted; but the corpuscular content is much less subject to variation than is that of the plasma.

The Cholesterol Content of the Blood after Splenectomy in Cases of Haemolytic Jaundice and Splenic Anaemia.

Although these findings in the different types and grades of anaemia appear by no means unequivocal, very striking results have been obtained in following the changes in the cholesterol content of the blood for several months after splenectomy in the three cases of haemolytic jaundice of the congenital type (acholuric family jaundice) and one of splenic anaemia. In addition to the cholesterol values, there are recorded in Table II the blood-counts and tests of the fragility of the red cells in the several cases. In the charts, where the abscissa represents the time in weeks before and after splenectomy when the blood was examined, the rise in plasma cholesterol is well shown, while it will be noted that the content of the corpuscles remains fairly constant and is practically within normal limits.

The following are brief clinical summaries of the four cases:

Case I. H. J. C., male aged 20, admitted to hospital complaining of pain in the abdomen of three months' duration, and of jaundice since the age of 3. A fairly well-nourished youth of a definite icteric tint. He was quite fit for his work as

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an engine-cleaner, except that during the last few months pain in the splenic region had caused him considerable inconvenience. Family history negative.

Stools of normal colour. Urine acholic and contained urobilin. Spleen much enlarged, extending down to the umbilicus.

On removal it was found to weigh 57 oz. Cholesterol before operation was 0.060 per cent., while twelve weeks afterwards it had increased to 0.160 per cent.

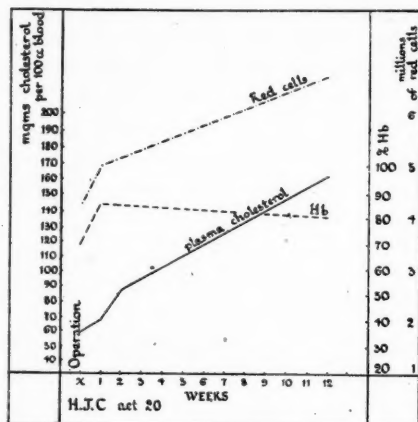


CHART I.

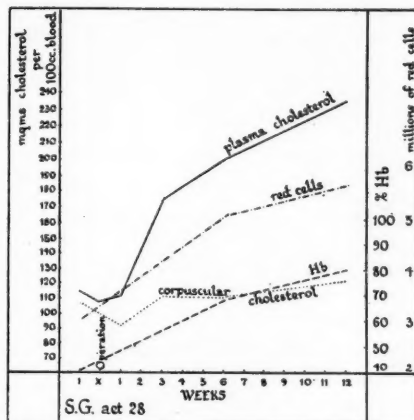


CHART II.

Case II. S. G., female, aged 28, admitted complaining of jaundice from birth and of attacks of pain in the abdomen associated with rigors and followed by deepening of the jaundice, on numerous occasions during the last seven years. In 1916 cholecystotomy had been performed, and a large number of small gall-stones were removed. Her condition did not improve, and one month later a cholecyst-enterostomy was performed, but with very little result. During the next two years (1917-18) the jaundice became worse and she had six severe attacks of rigors, pain, and deepening of the jaundice.

On admission to the Leeds General Infirmary, in January 1922, she appeared a well-nourished woman, deeply jaundiced.

The spleen was much enlarged, extending to within two inches of the anterior superior iliac spine, and was somewhat tender to palpation. The stools were cholic, while the urine was acholic and contained considerable urobilin. Patient's mother was said to have been slightly jaundiced since birth, and had died at the age of 24 of 'pernicious anaemia'.

After splenectomy the jaundice, &c., rapidly disappeared; she improved greatly in general health, and the cholesterol of the blood-plasma increased from 0.112 per cent. nine days before operation to 0.234 per cent. twelve weeks afterwards.

Case III. N. B., female, married, aged 28, came under observation for recurrent attacks of jaundice associated with abdominal pain since the age of 19. Two years ago enlargement of the spleen was noticed. She was treated as a case of splenic anaemia, receiving five X-ray applications to the spleen with no improvement. There has been a loss of two stones in weight during the last three years.

A somewhat thin and fragile-looking woman with a definite icteric tinge of the skin and sclerotics. Spleen much enlarged, two inches below umbilicus. Liver not palpable. Stools of normal colour; urine contained urobilin but not bilirubin.

She was profoundly anaemic (see blood-count) and on admission suffered from an irregular pyrexia with repeated rigors and associated jaundice. She had two blood transfusions before splenectomy was performed. At operation the gall-bladder was found distended with small calculi, but the patient's condition did not permit of their removal at this stage. The jaundice and urobilinuria disappeared within ten days of the removal of the spleen, while, as shown in the protocols, the cholesterol content of the plasma rose from 0.096 per cent. six weeks before the operation to 0.259 per cent., i. e. a figure almost three times as great and considerably above the normal, ten weeks after splenectomy.

This patient's father, J. W., aged 60, was also a typical case of haemolytic jaundice, with abnormal fragility of the red cells. He had been an in-patient eighteen years ago, and had been considered a case of splenic anaemia.

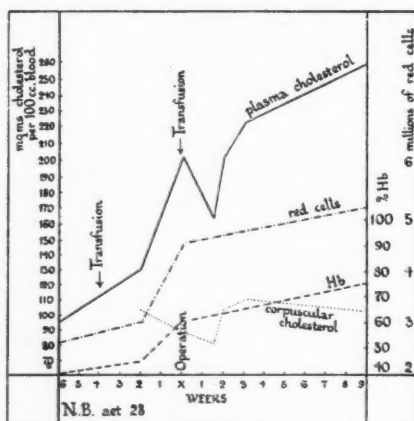


CHART III.

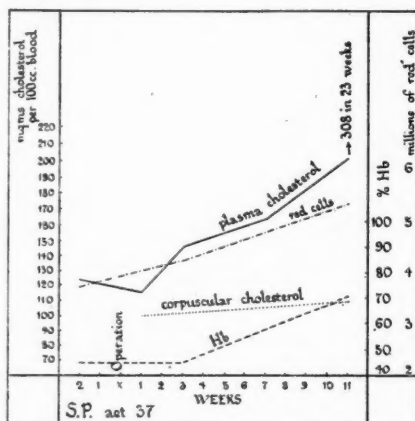


CHART IV.

Case IV. S. P., male, aged 37, admitted to hospital for recurrent attacks of haematemesis during the preceding six months. No previous ill health. Family history negative. On admission, anaemic with small rapid pulse. Spleen enlarged, $\frac{1}{2}$ inch below umbilicus. Fragility of blood-cells normal. He was diagnosed as suffering from splenic anaemia, and splenectomy was performed. The cholesterol of the plasma was normal before operation, viz. 0.150 per cent., with a red cell count of 3,500,000 and a colour index of 0.6. Thirteen weeks afterwards the cholesterol had risen to 0.308 per cent., and the patient's general condition had greatly improved.

From the records of the fragility tests in Table II, it will be noted that the low resistance of the red blood corpuscles remains practically unaltered three months after splenectomy, while that of the case of splenic anaemia is normal. A point of note is that in two of the cases (II and III) where it was possible to obtain samples of blood from the splenic vein, a greater degree of abnormal fragility was found than in the peripheral blood. As a control observation it may be mentioned that in a case of Banti's disease the red cells of the splenic blood were of the same normal resistance as were those of the median cephalic vein.

Another point of interest is that a marked rise in the cholesterol value of the blood-plasma was found in the case of N. B. (No. III) on the day following

transfusion of 600 c.c. of blood from a polycythaemic patient with a red cell count of $9\frac{1}{2}$ millions and the low cholesterol value of 0.074 per cent. So far we have not had the opportunity of repeating this observation.

Discussion.

These findings show conclusively that after removal of the spleen in acholuric jaundice, and doubtless also in splenic anaemia, there results a gradual but very considerable increase in the total cholesterol content of the plasma, and, in addition, a progressive improvement in the blood-count. At the same time, the rapid, indeed dramatic, disappearance of the general icterus after splenectomy is due to the elimination of the well-recognized activity of the spleen. We have already mentioned that cholesterol acts as an antihaemolytic agent against such substances as saponin, tetanolyisin, and cobra-venom. These observations raise the interesting question: Does the haemolytic function of the spleen depend on the rôle it plays in cholesterol metabolism?

So far as our data go, no changes have been noted in the red cells themselves. Their abnormal fragility in acholuric jaundice persists even four months after splenectomy. Giffin (6), in a study of corpuscular fragility in a series of cases of haemolytic jaundice in the Mayo Clinic, found a similar persistent lowered resistance in the majority of cases after operation. The resistance of the red cells in the case of splenic anaemia, even before operation, was greater than normal. Moreover, the cholesterol content of the corpuscles, as shown by the charts, remains exceedingly constant, and is a striking contrast to the progressive increase in that of the plasma. Nor would the data obtained by us in the cases of polycythaemia suggest any relation between the corpuscles themselves and the total cholesterol of the blood. Removal of the spleen appears, therefore, to be followed by certain changes in the lipoids of the plasma, and to be only indirectly related to any change in the red corpuscles themselves.

It is known that free cholesterol is present in both corpuscles and plasma, while cholesterol esters or 'bound cholesterol' is found in the plasma alone. It has not been possible so far in the present investigation to differentiate between free and bound cholesterol. Bloor (1), however, found the relation between free cholesterol and cholesterol esters to be within normal limits in all cases of anaemia. This is somewhat against the assumption that an abnormally large combination of cholesterol as ester is a factor in the production of anaemia.

There is some evidence, however, which suggests that there is an indirect association between splenic function and cholesterol metabolism. King (3) has determined the unsaturated fatty acid content of the blood (iodine value) in three cases of pernicious anaemia, and in two cases of acholuric jaundice, before and after splenectomy. He was stimulated to do this work by the suggestive results obtained by Faust and Tallqvist (7) in the anaemia produced by the tapeworm *Bothriocephalus latus*. These workers demonstrated the presence of a haemolytic substance in the worm, which they isolated and found to be cholesterol oleate. They further showed that the haemolytic properties were due entirely to oleic

acid, and that a strongly haemolytic chyle, owing its haemolytic properties to abnormal amounts of sodium oleate, could be obtained in dogs by feeding with oleic acid.

King, in the five cases associated with haemolysis examined by him, found a great increase in the unsaturated fatty acid content of the blood, in addition to the low cholesterol content of the plasma. He concludes (1) that there appears to be a parallelism between the unsaturated fatty acids in the blood and haemolysis, and (2) that this haemolysis is more marked because of the small amount of antihæmolytic substance, viz. cholesterol, present in the blood of these cases. His figures certainly show a very striking decrease in the unsaturated fatty acids after splenectomy in dogs, and in less degree in the one case of removal of the spleen in 'jaundice with enlarged spleen' in the human subject recorded in his protocols. But the method of obtaining the fatty acids from the blood used by King is not one which gives confidence either in the completeness of the extraction or in the prevention of oxidation of the fatty acids when isolated, and before their iodine value has been determined. The fact, also, that 100 c.c. of blood are required for the extraction renders investigation along these lines in the human subject wellnigh impossible.

Moreover, it has to be remembered that, as Bloor has pointed out, though cholesterol acts as an antihæmolytic agent against certain substances, there is no evidence to show that it protects against haemolysis by the unsaturated fatty acids, e.g. oleic acid. Nor is this increase in cholesterol and decrease in the unsaturated fatty acids, if confirmed, to be directly related. Lifschütz (8) believes that cholesterol can be synthesized in the body, and that it can be formed from oleic acid. He, however, presents no convincing evidence that he ever was able to isolate pure cholesterol. On the contrary, most of the recent work tends towards the views of Gardner (9) and his collaborators that it is highly improbable that cholesterol is synthesized in the body. In the healthy subject a cholesterol balance is established, all excess of cholesterol which is contained in the food being accounted for in the faeces.

Certainly there appears to be conclusive evidence of the great increase in the cholesterol of the blood-plasma after splenectomy in cases of hæmolytic jaundice, while there is no doubt that abnormal hæmolytic activity is eliminated by this operation. So far there is no evidence as to what extent and in what way this hypercholesterolaemia is related to the cessation of splenic function.

Conclusions.

1. The cholesterol content of the blood-plasma is diminished in anaemic conditions, although the decrease may not be striking unless the red cell count is less than 50 per cent. of the normal. In the various grades of anaemia there is some decrease in the cholesterol of the red cells, but the corpuscular content is much less subject to variation than is that of the plasma.

2. There is no noteworthy difference in the blood cholesterol in cases of secondary and of pernicious anaemia; nor do the leucocytes appear to be correlated to variations in the plasma cholesterol.

3. After removal of the spleen in cases of familial acholuric jaundice and splenic anaemia, there results a gradual but very considerable increase in the total cholesterol content of the blood-plasma, while that of the corpuscles varies within a relatively narrow range. Thus in the cases of haemolytic jaundice the cholesterol values of the plasma, three months after splenectomy, were 0.160 per cent., 0.234 per cent., and 0.259 per cent. as compared with 0.060 per cent., 0.112 per cent., and 0.094 per cent. before operation.

4. Although splenectomy is followed by a progressive improvement in the red cell count, the increase in the lipoids of the plasma appears not to be related to any change in the corpuscles themselves. So far as our data go, their abnormal fragility in haemolytic jaundice persists three months after removal of the spleen, although the icteric tint and the urobilinuria disappear within ten days of operation.

5. There is no evidence that an abnormally large combination of cholesterol as ester is a factor in the production of anaemia, while the decrease in the unsaturated fatty acids of the blood following splenectomy in cases of anaemia, recorded by King, even if confirmed, does not appear to be related to the increase in cholesterol.

6. The evidence pointing to a very considerable increase in the cholesterol of the blood-plasma after splenectomy in haemolytic jaundice seems conclusive, but the relationship of this hypercholesterolaemia to the cessation of splenic function is quite undefined.

It is with pleasure that we acknowledge our indebtedness to Sir Berkeley Moynihan, Bart., for granting us permission to make these observations on cases before and after operation by him, and for access to the clinical records. Our thanks are due to the physicians of the Leeds General Infirmary for their courtesy in permitting the investigations on cases of anaemia under their care, to Professor M. J. Stewart, in whose department the work has been carried out, and to Dr. H. H. Gleave for a number of the blood-counts.

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QUINIDINE IN THE TREATMENT OF AURICULAR FIBRILLATION¹

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I. *Introduction.*

IN a recent paper (1) the writer published twenty cases of auricular fibrillation treated with quinidine, in seventeen of which normal rhythm was restored.

Since then these twenty cases have been followed up, and several of them have now been under observation for over a year. Twenty-five additional cases have been treated, and the writer feels that he now has sufficient material on which to base certain conclusions.

Meanwhile the literature on the subject has grown enormously, especially in America and on the Continent. A full summary of it in a paper such as this would be impossible, and in the present condition of the subject would serve no useful purpose. The work of others, however, is referred to to supplement the writer's own observations, but the conclusions drawn are based on his personal experience only. As the evidence on which they are formed is given, their value will be judged when the literature comes to be reviewed.

Since his last paper was written, owing to the kindness of Dr. Brander, the writer has had access to the wards of a large London infirmary. An arbitrary age-limit of 65 has been adopted, and cases in which partial compensation could not be restored with digitalis, and in which chronic oedema persisted, have not been treated with quinidine. Not that the drug may not benefit such cases, but because it has been thought wiser to work out the value and risks of quinidine treatment in patients better able to stand the possible dangerous eventualities that are known occasionally to occur. Apart from this no selection of cases whatsoever for the purposes of this research has been exercised. Provided that compensation at rest in bed could be at least partially restored with digitalis, all patients with auricular fibrillation admitted in rotation to the wards of a London general hospital and a London infirmary have been treated with quinidine, irrespective of the nature and extent of the pathological lesions of the heart, the duration of cardiac symptoms, and the coexistence of other morbid

¹ This communication, together with case reports and tracings, was accepted as a thesis for the degree of M.D. in the University of Cambridge, January, 1923.

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conditions. All cases received an initial course of digitalis, and therefore some time was allowed for spontaneous return to normal rhythm to occur. This only occurred in one case (XLV), which happens to be the only case of the series with auricular fibrillation definitely of the paroxysmal type. No case of auricular fibrillation associated with an acute infective disease has come under observation, but one case (XII) of subacute bacterial endocarditis has been treated with quinidine.

The general methods of procedure have remained substantially the same as formerly, and an effort has been made to adopt standard systems of dosage so as to obtain comparable results. The electro-cardiograph has been available to elucidate some of the rhythms, and for assistance with this instrument I am indebted to Dr. John Parkinson. Unfortunately it has not been possible to take electro-cardiograms systematically, and as before main reliance has been placed on polygraphic tracings.

The quinidine employed has been the sulphate supplied by Messrs. Whiffen and Sons. The drug has been administered in powders or tablets, and not in capsules. Lewis (2) has shown that commercial quinidine contains 20 per cent. of hydroquinidine, but as the latter has a slightly more powerful action than quinidine itself the purification of the commercial product for therapeutic purposes is unnecessary. All doses in this paper are expressed in grains, and may be converted into grammes by multiplying by the factor 0.06.

Forty-five unselected cases of auricular fibrillation have now been treated with quinidine, and in thirty-seven (82 per cent.) normal cardiac rhythm has been restored.

Tables summarizing the histories and clinical conditions of the patients treated, together with the results obtained and the observations recorded, are given in an Appendix.

The cases are classified into the three same groups as previously. Group A includes those cases in which normal rhythm, having been successfully restored, persisted until the patient was discharged from hospital. Group B includes those cases in which only a transitory return to normal rhythm was effected, and in which relapse into fibrillation occurred prior to discharge. Group C includes those cases in which quinidine entirely failed to restore normal rhythm. Group A is divided into Sub-groups I and II. Sub-group I includes those cases in which auricular fibrillation had been of comparatively short duration, and which, prior to admission to hospital when they received quinidine, had been given no digitalis treatment. Sub-group II includes those cases in which auricular fibrillation had been of comparatively long duration. These cases had received definite digitalis treatment prior to their admission to hospital when they first received quinidine therapy. In Sub-group II it is possible to compare the relative merits of quinidine and digitalis in the treatment of auricular fibrillation. In Sub-group I it is only possible to judge the value of restoration of normal rhythm as a therapeutic measure.

The Wassermann reaction has been performed in all cases, but the results

obtained before and after quinidine administration have been somewhat conflicting. It seems possible that quinidine may exert some influence on haemolysis. No definite statement can yet be made, and the average results are given for what they are worth. This question remains one for future investigation.

II. *Methods of Administration and Dosage.*

All cases on admission have first been treated with digitalis until compensation was restored as much as possible. Digitalis has then been discontinued altogether and quinidine administered. In all but the first seven cases an arbitrary but standard system of dosage has been adopted. Quinidine gr. v, six-hourly, was given to start with and continued for seventy-two hours (12 doses). The dosage was then increased gr. iv per diem until either normal rhythm was restored or until further administration of the drug was contra-indicated. The patient thus received gr. vi six-hourly on the fourth day, gr. vii six-hourly on the fifth day, and so on. In all cases the drug has been pushed to the maximum amount it was thought safe to administer—that is to say, until severe toxic symptoms or signs and symptoms of cardiac failure were observed. In the present state of our knowledge we do not know if relapse into fibrillation will necessarily occur when quinidine is discontinued. In this series of cases, except when the patient would not bother to take it, quinidine gr. v, twelve-hourly or eight-hourly, has been continued indefinitely according to the needs of each particular case. When normal rhythm had been restored, the dosage was kept constant either at that level or slightly above it for a few days, and then decreased gr. iv per diem until the prophylactic dosage was attained.

Lewis (2) has shown that the maximum effect of the oral administration of a single dose of quinidine in decreasing the rate of the auricular oscillations on the electro-cardiogram is obtained at the end of two hours. Accordingly, to two cases (XXIV, XXVIII) of this series in which the ordinary standard system of dosage failed to restore normal rhythm, a second course of quinidine was administered at a 'doubled standard rate'. Twelve gr. v doses were given at three-hourly intervals, and then the dosage of the drug was increased by gr. iv after every four doses—that is to say, the patient received twelve gr. v doses, four gr. vi, four gr. vii, and so on, all doses being separated by three-hourly intervals. In Case XXIV normal rhythm was restored by this method when the ordinary standard system of dosage had failed. But in Case XXVIII it also failed to produce the desired result. The remaining seven unsuccessful cases had reacted too severely to quinidine to justify any further administration of the drug.

Intravenous injections of quinidine have been tried by Hass (3), but have been followed by severe collapse, and are not recommended by Clerc and Pezzi (4) and others.

III. *Digitalis and Quinidine.*

It has been the writer's practice to restore compensation as completely as possible with digitalis before quinidine was first administered. This has been the procedure with the majority of other workers, but Hamburger and Priest (5) have given quinidine during periods of decompensation with satisfactory results. It would seem more rational to restore compensation with digitalis prior to quinidine administration, because by so doing the patient is put in the best possible condition to stand the possible ill effects produced by the drug. The writer has made it a rough rule, except in cases of exophthalmic goitre, to reduce the ventricular rate below 80 before starting quinidine.

The question now arises as to whether digitalis, given simultaneously with quinidine, facilitates or antagonizes the action of the latter drug in restoring sino-auricular rhythm. Clinical research of this nature depending largely on the statistical method, every effort has been made to keep the few factors under our control constant. Except in a few cases, therefore, digitalis has not been given simultaneously with quinidine lest the issue might be confused. Accordingly little evidence has been obtained on this particular point.

On the whole the unsuccessful cases of Group C received shorter courses of digitalis than the successful cases in Groups A and B. In three of the former, however (VII, XIV, XVI), the simultaneous administration of digitalis towards the end of the quinidine course failed to facilitate the action of quinidine in restoring normal rhythm. Of the successful cases, digitalis was administered continuously throughout the quinidine course in Case IX and at the beginning of the course in Case IV. Case VI received one dose of digitalis on the fifteenth day of the quinidine course, and two hours later normal rhythm was restored. In Case V the administration of quinidine following a short course of digitalis (two days) failed to restore normal rhythm, but a second course of quinidine following a prolonged course of digitalis produced a transitory return to normal rhythm. A third course of quinidine, however, in conjunction with digitalis failed to repeat the desired result.

Frey (6) states that the action of quinidine is impeded by the simultaneous administration of digitalis. But Lewis and his co-workers (2) have restored normal rhythm successfully by giving the two drugs together. They have shown that quinidine causes a fall, but digitalis a rise, in the rate of auricular oscillations which are seen on the electro-cardiogram. Moreover, they have tested this particular point by observing in the same patient the fall in auricular rate produced by the same dose of quinidine before and after digitalization. They found that the lowest auricular rate produced by quinidine is lower in the undigitalized than in the digitalized heart. They conclude, however, that the slight disadvantage to the quinidine reaction which follows digitalis therapy is more than counteracted by the benefit of the control of ventricular rate which is obtained. It would therefore seem rational to give quinidine after a thorough initial course of digitalis, and only administer digitalis simultaneously with

quinidine if the ventricular rate begins to rise too high. If this method is practised, it should be possible to continue quinidine over longer periods, as the onset of ventricular tachycardia and consequent cardiac symptoms should be delayed.

In Case XXVII, a female with rheumatic heart disease, mitral stenosis, and high blood-pressure, large doses of quinidine (180 gr. in all, maximum dosage gr. ix, six-hourly) failed to restore normal rhythm, and the drug then had to be discontinued on account of increased cardiac and general toxic symptoms. A fairly long course of digitalis now caused coupled ventricular beats, but no other signs or symptoms of digitalis poisoning. Digitalis was now discontinued and quinidine immediately readministered. After the second 5 gr. dose of quinidine the patient died suddenly. Post-mortem examination showed chronic valvular lesions, but failed to reveal the cause of sudden death. To give quinidine immediately after digitalis had produced coupled beats was undoubtedly a therapeutic mistake on the writer's part. But it would seem that in this case death should be attributed at least as much, if not more, to digitalis than to quinidine.

This experience has made the writer rather averse to the simultaneous administration of two drugs our knowledge of the pharmacology of which is after all only elementary. Accordingly, in general this has not been practised, and in the present state of our knowledge is not advised.

IV. *Successful Quinidine Treatment and its Relationship to the Pathological Condition of the Heart and the Clinical Condition of the Patient.*

It is extremely important from the point of view of practical therapeutics that we should be able to foretell the type of case in which a successful physiological action of quinidine can be reasonably expected. Unless this can be done, large numbers of patients will be submitted to the dangers and discomforts of treatment in vain. The following factors must be taken into consideration :

- (1) Total duration of cardiac symptoms.
- (2) Duration of the disorder of rhythm.
- (3) Nature of the pathological process affecting the heart.
- (4) Presence or absence of active disease process.
- (5) The degree of compensation or decompensation, i.e. the exercise tolerance of the individual.
- (6) The size of the heart.
- (7) The valvular lesions.
- (8) Age and sex of the patient.

These different factors will now be considered in turn, and their relationship to the probability of quinidine producing a successful physiological result discussed. In such a small series of cases as forty-five it is dangerous to draw any conclusions from correlations. Nevertheless, conclusions drawn in this way will be given tentatively for what they are worth.

On the whole it may be said that cases of heart disease of short duration

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with auricular fibrillation of recent onset have reacted most successfully to quinidine. A smaller dose of the drug is usually required to restore normal rhythm in these cases than in others. The duration of the disorder of rhythm seems to be a more important factor from this point of view than the total duration of cardiac symptoms.

In the thirty-seven successful cases in which sino-auricular rhythm was restored the aetiological factors in the pathological condition of the heart were assessed as follows:

Rheumatism only	20
Rheumatism and cardio-vascular degeneration	5
Rheumatism and obesity	2
Rheumatism, cardio-vascular degeneration, and hyperthyroidism	1
Rheumatism and syphilis	3
Rheumatism and infective endocarditis	1
Cardio-vascular degeneration only	1
Exophthalmic goitre only	2
Exophthalmic goitre and syphilis	1
Nil diagnosed	1
	<hr/> 37

In the eight unsuccessful cases:

Rheumatism only	5
Cardio-vascular degeneration only	1
Rheumatism and obesity	1
Obesity only	1
	<hr/> 8

With the exception therefore of the fact that all the four cases of auricular fibrillation associated with exophthalmic goitre reacted successfully to quinidine, no definite correlation between the probability of success and the aetiological factors can be shown.

The presence or absence of active disease is always difficult to determine. It is however likely to be present in the degenerative and syphilitic cases, and these reacted as well or better to quinidine than the rheumatic cases of long standing. The one case of infective endocarditis associated with fibrillation had normal rhythm restored by a very small dose of the drug. In both cases of auricular fibrillation associated with the active stage of exophthalmic goitre normal rhythm was successfully restored. Also, if the onset of auricular fibrillation affords evidence of active myocardial change, the ease with which cases of recent onset respond to quinidine again suggests that cases with active myocardial change respond particularly readily.

Decompensation is generally said by other workers to affect the expectation of a successful result from quinidine unfavourably. But in this series of cases compensation in all cases has at least been partially restored with digitalis, and therefore no evidence on this particular point has been obtained.

On the whole large hearts react poorly to quinidine. This is shown by the large size of the hearts in Group C. Also, large hearts usually required larger doses of quinidine to effect the restoration of normal rhythm than did those of smaller size.

The poor results obtained in the young patients of this series are remarkable. The only two cases under the age of 26 years were failures as far as the restoration of normal rhythm was concerned. All the unsuccessful cases in Group C are relatively young. Certainly age up to 65 is no contra-indication in itself to quinidine treatment.

The presence or absence of valvular lesions seems to bear no relationship to the probability of quinidine effecting the restoration of normal rhythm. In all three cases of aortic incompetence sino-auricular rhythm was restored, and cases of mitral stenosis and those without valvular lesions reacted or failed to react in approximately equal proportions.

The maximum amount of quinidine which was necessary to restore normal rhythm was 392 gr. with a maximum dosage of gr. xiv, six-hourly (Case XLIII). This occurred on the twelfth day of treatment, but relapse occurred a few days later.

The minimum amount of quinidine which effected this result was in Case XLV, a male with exophthalmic goitre and auricular fibrillation essentially of the paroxysmal type. Sino-auricular rhythm returned six hours after the administration of one 5 gr. dose.

In two cases 15 gr. restored normal rhythm—in Case XII, a male with infective endocarditis, and in Case XXIX, a female with a rheumatic heart, mitral stenosis, and chronic high blood-pressure.

In Case XIV 862 gr. of quinidine with a maximum dosage of gr. xv six-hourly failed to restore normal rhythm on the 26th day, either alone or combined with digitalis.

Leaving out of consideration the first six, which were treated before a standard system of dosage had been adopted, it is interesting to compare the maximum six-hourly doses, which were effective in restoring normal rhythm in the remaining thirty-one cases. A maximum dosage of gr. v restored normal rhythm in eleven cases, gr. vi in three cases, gr. vii in two, gr. viii in one, gr. ix in two, gr. x in three, gr. xi in four, gr. xii in two, gr. xiv in two, gr. xvi in one. These findings are suggestive, but again the danger of drawing conclusions from correlations in a small number of cases must be emphasized. They suggest that cases that react to quinidine may be divided approximately into two groups, those that react to small and those that react to large doses of the drug. Lewis, Drury, Ilescu, and Wedd (7) have shown that quinidine increases the length of the refractory period of cardiac muscle and decreases the rate of conduction. These two actions of quinidine are antagonistic as far as bringing the circulating wave which underlies auricular fibrillation to an end. If these two actions of quinidine are exercised to the same degree, the gap between the head and tail of the circulating wave remains the same, but the rate of circulation is slowed. If, however, the refractory period is increased out of proportion to the conductivity, the gap is bridged and fibrillation ceases. Possibly in the group of cases that reacts to small doses of the drug the effect of quinidine on the refractory period predominates, while in the group which reacts to large doses the increase

in the refractory period and the diminution of conductivity advance *pari passu* until large doses have been given. Then only does the effect on the refractory period predominate over that on conductivity so that fibrillation ceases. In those cases in which quinidine fails to restore normal rhythm it must be supposed that this latter effect fails to occur within the limits of tolerance of the drug.

But apart from theoretical considerations these observations are of some practical importance. The majority of cases which react to quinidine react to small doses. As the dosage is increased without a successful result having been obtained, the expectation of restoring normal rhythm becomes progressively less. Also, it may be stated that on the whole the probability of relapse occurring is greater in those cases which react to large than in those cases which react to small doses. The risks of quinidine treatment other than embolism increase proportionally with the size of the dose employed. Therefore in practice, as we wish to get the maximum of therapeutic successes with the minimum of ill effects, it would be well to limit the maximum dosage on the standard system to gr. viii, six-hourly or thereabouts.

The best method of administering quinidine, the action of which depends on the interrelationship of two antagonistic factors, will require much further investigation. This is exemplified by the fact that if a certain quantity of the drug given in a certain way produces a certain result, sino-auricular rhythm or auricular flutter, it does not follow that after relapse has occurred the same amount of the drug given in a different or even in the same way will produce the same result. Thus in Case XXII 55 gr. of quinidine produced auricular flutter. Quinidine was discontinued and relapse occurred. Twenty grains now produced normal rhythm which was not preceded by flutter. In Case II 95 gr. produced normal rhythm alone, but after relapse had occurred 50 gr. produced normal rhythm preceded by flutter. In Case V 75 gr. restored sino-auricular rhythm, but after relapse had occurred 706 gr. given in a slightly different way failed to produce the same result. In Case XXXIII 60 gr. produced normal rhythm, but after relapse 509 gr. given in the same way produced flutter but no return to normal rhythm. But, generally speaking, when relapse occurs after successful quinidine therapy, normal rhythm can usually be quickly restored by slightly increasing the dosage of the drug.

V. *The Ill Effects of Quinidine Administration.*

These may be best classified as follows:

- (1) General symptoms of quinidine intoxication.
- (2) Embolism consequent on restoration of auricular function.
- (3) Symptoms due to the toxic action of the drug on the myocardium.
- (4) Symptoms due to disturbance of the cerebral circulation.
- (5) Respiratory paralysis.

(1) *General symptoms of quinidine intoxication.* With the exception of those cases in which normal rhythm has been quickly restored, symptoms of quinidine intoxication have been the rule. The commonest of these have been gastro-intestinal: nausea, anorexia, diarrhoea, abdominal pain, and vomiting. Headache has been frequent and excessive sweating fairly common. During the early stages of administration of the drug these symptoms have usually passed off without any reduction in dosage. During the administration of larger doses, these symptoms have occasionally been so severe as to necessitate the abandonment of further treatment. More usually quinidine has had to be discontinued on account of increased cardiac symptoms rather than on account of general toxic symptoms. In Case XV small doses of the drug led to excessive vomiting. The drug was pushed, and following the restoration of normal rhythm a syncopal attack occurred in which the patient nearly died. Very sudden attacks of abdominal pain have been not uncommon, and in Case XLIII such an attack associated with excessive vomiting led to dangerous collapse.

Visual symptoms, mistiness of the eyes, and transient attacks of failing vision have been occasionally associated with large doses of the drug. In all cases the visual fields to ordinary clinical tests remained normal and no retinal changes were observed. These attacks have usually been associated with increased ventricular rate and fall of blood-pressure. Quinine being known to cause amblyopia, symptoms of this kind of any degree of severity have been regarded as an absolute contra-indication for further administration of quinidine.

A papular scarlatiniform rash appeared in two cases (V, VII), and a rash not unlike rubella in one (XLIII). An urticarial rash was associated with the administration of quinidine in Case XL, and in Case XXXVII two attacks of inflammatory oedema of the face occurred during the prophylactic administration of the drug.

Case XLI developed glycosuria twenty-one days after quinidine had been discontinued.

A mild degree of pyrexia has been associated with the administration of the drug in ten cases. This has coincided so frequently with the maximum of quinidine administration that the writer definitely attributes it to the action of the drug. Whether quinidine exerts a direct action on the heat-regulating centre or produces this effect by lighting up a low-grade infection is uncertain. All these patients were relatively young, and nine of them were definitely rheumatic. One of them also developed a catarrhal pharyngitis.

Case XVIII developed a cervical adenitis during treatment, for which no cause could be found.

Case XXXVII developed laryngitis without pyrexia, also during the maximum of quinidine administration.

The large majority of cases have tolerated the prophylactic administration of quinidine over long periods without symptoms. Mild toxic symptoms have appeared in a few cases, but have usually disappeared when the bowels were judiciously regulated.

2. *Embolism consequent on restoration of auricular function.* Embolism occurred shortly after the restoration of normal rhythm in four cases (I, III, XX, XXXVI) and probably in two others. In Case I simultaneous infarction of kidney and lung took place, and when relapse into fibrillation followed, popliteal embolism occurred. Fatal pulmonary embolism occurred in Case XXXVI, but autopsy showed that the embolus was derived from thrombosis in the iliac veins and not from the auricular appendices. Excluding this case, which is irrelevant to the present discussion, the other three all had mitral stenosis and were cases of auricular fibrillation of 18-30 months' duration in which several previous attacks of decompensation had occurred, but in only one of these three cases (XX) had previous embolism taken place. In two cases (VI, XII) embolism had previously occurred, but it did not follow the restoration of normal rhythm.

That the auricle, when it first starts to contract as a whole after several months of fibrillation, should expel thrombi into the systemic or pulmonary circulations is not surprising. Thrombosis in the auricular appendices is particularly likely to occur in cases of long-standing fibrillation in which previous attacks of decompensation have occurred. But the incidence of embolism in the early cases of this series has been particularly high, and the recent cases and the results of other workers would show that the risk of embolism is not as great as Ellis and the writer (8) first supposed.

Thus Viko, Marvin, and White (9) have compared the frequency of untoward results in 452 cases of auricular fibrillation treated with quinidine and reported in the literature with 200 cases of fibrillation to which quinidine was not given. They found that the percentage in which embolism occurred was equal in the two series, but that sudden death occurred more frequently under quinidine.

Similarly Levy (10) states that out of 50 consecutive cases, half of which were treated with quinidine and the other half with digitalis only, embolism occurred in one case in the former group, but in five cases of the latter.

Oppenheimer (11) has treated 56 cases without a single instance of embolism. Two cases had previously suffered from cerebral embolism, but nothing of this nature occurred when normal rhythm was restored.

The writer still believes that embolism must remain a real danger in the treatment. Though no fatal case has occurred in this series, deaths from this cause have been reported by Carter, Dieuaide, and Burwell (12), Levy (10), Sappington (13), and others. It is at least rational and certainly on the safe side at present to regard the previous occurrence of embolism in cases of auricular fibrillation as a contra-indication for quinidine treatment.

3. *Symptoms due to the toxic action of the drug on the myocardium.* In seven out of the eight unsuccessful cases in Group C to which large doses of quinidine were administered, definite appearance or increase of pre-existing cardiac symptoms was observed. The same was observed when large doses of quinidine were necessary to restore normal rhythm in four of the successful cases (XV, XXI, XXIV, XXIII). Most of these patients gave long histories of cardiac symptoms, had large hearts, and were poorly compensated. These symptoms

were invariably associated with ventricular tachycardia, and might possibly be attributed to this alone. If this is so, the simultaneous administration of digitalis in these cases, as already suggested, might render it possible to carry quinidine treatment farther. But it seems more likely that the direct action of quinidine on the myocardium causes a lowering of the functional efficiency of the heart apart from the tachycardia which is produced.

Fatal cases due to rapid increase in decompensation during quinidine treatment have been reported by Benjamin and v. Kapff (14), v. Bergmann (15), and others, but no case of the kind has come under the observation of the writer.

Cases of sudden death occurring during the administration of quinidine, either before or after the restoration of normal rhythm and not attributed to embolism, have been reported by Hewlett and Sweeney (16), Levy (10), Hay (27), and others. The writer has had one such fatality² (Case XXVII) which was undoubtedly due to the combined toxic action of digitalis and quinidine on the myocardium, autopsy failing to reveal the cause of sudden death. A fatal ending in similar circumstances almost occurred in Case XV. Sixteen hours after the return of normal rhythm, when taking quinidine gr. vii six-hourly, she became suddenly unconscious, with apnoea, pulselessness, and profound cyanosis. She recovered gradually, but had another similar but less severe attack a few hours later. During this period the pulse became completely irregular, but normal rhythm returned the following day despite the fact that quinidine had been discontinued with the onset of the attack. Following the attacks the patient became extremely restless and shrieked incessantly, but the following day had complete amnesia for all that had occurred. The actual explanation of the attack was doubtful, but it was definitely syncopal in nature and partook of none of the features of respiratory paralysis. Following the attack the *a-c* interval was slightly prolonged. It is considered, however, that this was more likely due to the asphyxial conditions maintaining during the attack, than that the attack itself was due to acute heart-block. The cerebral symptoms must be attributed to a similar cause. It is interesting to note that this particular patient vomited copiously at the outset of quinidine administration. The drug was pushed, however, and she seemed to develop tolerance. Idiosyncrasy towards the alkaloid suggests itself.

The pathogenesis of death in these fatal cases has received various explanations, but, as might be expected, autopsy, save to exclude embolism, has yielded no information. Heart-block, ventricular fibrillation, vagal stimulation, and failure of the sino-auricular node to begin initiating stimuli when fibrillation ceases have all been suggested.

Lewis (2) has shown that quinidine in therapeutic doses slightly increases the conduction time in the *a-v* bundle. In only two cases of this series, Case XV already referred to and Case XXVI, has an *a-c* interval of greater length than 0.2 second followed the return of normal rhythm. A transient attack of 1:3 heart-block was observed in Case I following quinidine and digitalis.

Hewlett and Sweeney (16) report one case of heart-block following quinidine

² See Section III, p. 208.

treatment, and two cases of bundle branch block in similar circumstances are reported by Viko, Marvin, and White (9). Seeing that quinidine and digitalis both depress bundle conductivity, acute heart-block seems a not unlikely explanation of some of these fatalities, and particularly of the death of Case XXVII. This is an additional reason why quinidine and digitalis should not be administered together as already advised. Pre-existing heart-block is certainly a contra-indication for quinidine treatment. Bock (17) administered quinidine to two cases of auricular fibrillation with complete *a.-v.* block. In both cases the Stokes-Adams syndrome returned. Groedel (18) gave quinidine to a man with complete heart-block and he died suddenly on the fourth day.

4. *Symptoms due to disturbances of the cerebral circulation.* In two cases in which quinidine failed to restore normal rhythm (XIV, XXXIV) and in one of the successful cases (XXVI) cerebral symptoms were observed. In the former they occurred during the maximum of quinidine administration, but in the latter a few hours after normal rhythm was restored. Case XIV suddenly 'felt funny and lost herself', and was said to look 'as if in a kind of faint'. Case XXXIV suddenly 'felt funny, saw double, seemed to lose herself, and then shrieked out'. Case XXVI, according to the nurse's account, rolled her eyes, frothed at the mouth, and became unconscious. A few minutes later she became extremely restless, shrieked out wildly, and had to have morphia. The following day she had complete amnesia for the attack.

In none of these attacks were definite paralyses, involuntary movements, or squints observed. Following them no abnormal physical signs were elicited on examination of the nervous system. Seeing that quinidine administration is frequently associated with fall in blood-pressure and that sudden alteration in cardiac rhythm might be expected to produce a similar result, and in view of the transient nature and the particular times at which they occurred, it seems more reasonable to attribute these attacks to interference with the cerebral circulation rather than to embolism or the direct action of the drug on the cerebrum.

5. *Respiratory paralysis.* Frey (19) has reported cases of sudden respiratory paralysis associated with quite small doses of the drug. These patients were successfully revived with artificial respiration and stimulants. Schott (20) has demonstrated respiratory paralysis in dogs under the action of quinidine. No cases of this kind have been observed in the present series.

VI. Quinidine and Cardiac Rhythm.

Lewis has shown that the transition from auricular fibrillation to normal rhythm under quinidine takes place usually through a condition of impure and occasionally through pure flutter. As the refractory period of the auricular musculature increases, the transmission intervals lengthen and the rate of conduction of the excitatory wave is diminished. The auricular oscillations on the electro-cardiogram become more regular and less frequent.

In nine cases of this series the ventricular action has become progressively more regular and a condition of impure flutter was presumed to exist. In

four cases (I, XIX, XXX, XXXII) pure auricular flutter preceded return to sino-auricular rhythm. In two cases (I, XXIII) relapse into fibrillation was preceded by pure flutter. In Case I, in which normal rhythm had been previously restored, quinidine administered as a prophylactic seemed to cause auricular flutter which digitalis converted into normal rhythm with a transient attack of 1:3 heart-block.

Extra-systoles. Out of the 37 successful cases of this series, in 19 extra-systoles have been observed interrupting normal rhythm at some time or another after its return.

In five cases (XIII, XXIX, I, IV, XLII) occasional auricular extra-systoles, and in three cases (XXX, XXXII, XLV) sequences of auricular extra-systoles, occurring at regular intervals after every second, third, or fourth normal beat, have been recorded. In two of the former only were these premature beats observed immediately after the return of normal rhythm, while in the remainder they appeared some time during the prophylactic administration of the drug. In one case (XLV) they disappeared as the dosage of quinidine was reduced, but relapse into fibrillation then occurred. In one other of these cases only has relapse into fibrillation so far taken place.

In Case XI, some time after the restoration of normal rhythm, and during the temporary suspension of quinidine on account of toxic symptoms, occasional isolated auricular extra-systoles were observed introducing short sequences of regularly spaced ventricular extra-systoles. When quinidine was readministered both varieties of these premature beats disappeared.

In Case X, when normal rhythm was first restored it was frequently interrupted by regularly spaced ventricular extra-systoles occurring late in diastole after every normal beat. When the dosage of quinidine was reduced these extra-systoles occurred much less frequently and progressively earlier in diastole until they were eventually interpolated between successive normal beats. When the drug was discontinued altogether these premature beats vanished, but a little later auricular extra-systoles made their first appearance, and introduced short sequences of regularly recurring ventricular extra-systoles. Quinidine was now readministered as a prophylactic, but the auricular extra-systoles persisted, paroxysms of tachycardia supervened, and relapse into auricular fibrillation followed.

In Case XXXI both auricular and ventricular premature beats have been observed during the prophylactic administration of quinidine, but no relationship between their appearance has hitherto been observed.

In the remaining seven out of the nineteen cases in which extra-systoles were observed their point of origin could not be determined, but in one case only (XXXV) did they occur immediately when normal rhythm was restored.

In Case XXV the return of normal rhythm was associated with the phenomenon of escaped ventricular beats. These escaped ventricular beats disappeared as the dosage of the drug was reduced, but sequences of ventricular extra-systoles have since occurred at frequent intervals.

In Case XLIII, when sino-auricular rhythm was first restored, for short periods at a time, the polygraph tracings showed sudden disappearance of *a*-waves, doubling in the height of the *c*-waves, without alteration in the radial rate. There are two possible explanations of this phenomenon, namely, the sudden inception of nodal rhythm or ventricular escape.

The pathogenesis of extra-systoles remains obscure and their relationship to circus movement requires investigation. The fairly frequent occurrence of sequences of regularly spaced extra-systoles following the return of normal rhythm is suggestive. That premature auricular contractions frequently precede the onset of auricular fibrillation is well known. But it is equally true that auricular extra-systoles can occur for years in patients who never develop auricular fibrillation. Quinine and quinidine are regarded by most workers as exercising a depressant influence on the excitability of the myocardium. Smith (21) and others have shown that quinidine will frequently abolish extra-systoles. From the point of view of practical therapeutics with which we are immediately concerned, what we want to know particularly is whether the appearance of extra-systoles is an indication that relapse into auricular fibrillation is imminent, and therefore if the dosage of the drug should be increased. The evidence given above is conflicting, but the absence of premature beats interrupting normal rhythm in Group B, in which relapse into fibrillation soon occurred, is striking. The writer inclines to the view that the appearance of auricular extra-systoles following the return of normal rhythm does not suggest that relapse is particularly likely to occur, and is therefore no indication for increasing the dosage of quinidine. Even if quinidine is active in suppressing extra-systoles, these rarely cause symptoms necessitating treatment, and therefore in general the drug should not be administered for this purpose alone.

The large majority of premature beats recorded in this series of cases have been auricular in origin. Lewis (2, 22) and Levy (10) regard the occurrence of multiple ventricular extra-systoles during quinidine treatment to be an absolute indication for the discontinuation of the drug. This phenomenon is known to frequently precede ventricular tachycardia and ventricular fibrillation. The ventricular extra-systoles to which these writers particularly refer are those ectopic ventricular beats which occur most frequently at the height of the auricular reaction before normal rhythm is restored—that is, when the auricular rate is reduced to its lowest during the maximum of quinidine administration. These extra-systoles will usually be missed on polygraphic tracings only, and, as they may be a danger signal of impending ventricular fibrillation and death, the importance of frequent electro-cardiograms during treatment is apparent.

VII. *The Effect of Quinidine on Pulse-rate, Blood-pressure, and Fluid Output.*

1. *Pulse-rate.* During the administration of quinidine workers with the electro-cardiograph have shown that as the auricular rate falls the ventricular rate rises in proportion. Lewis (2) attributes this to two causes, increased conductivity

of the bundle consequent on the slowing of the auricular rate and the vagal paresis which quinidine is known to produce.

In the majority of both the successful and unsuccessful cases of this series a progressive rise in the ventricular rate as judged by auscultation at the apex beat has been observed during treatment with the drug.

The radial rate usually rises to a less extent—that is to say, a pulse deficit appears or a pre-existing deficit increases. With the onset of sino-auricular rhythm the ventricular rate usually dropped to normal, but in a few cases a higher rate persisted. In these cases the expectation of a successful therapeutic result being obtained is poor. In many cases, either immediately or shortly after the return of normal rhythm, a definite bradycardia (pulse-rate below 60) appeared, and usually continued until the patient was allowed up. This bradycardia has not been associated with depressed *a.-v.* conduction and is no indication for discontinuing the drug. During the prophylactic administration of quinidine the pulse-rate usually remains within normal limits.

2. *Blood-pressure.* An approximate method of measuring the systolic and diastolic blood-pressure during auricular fibrillation has been described (1). During the tachycardia associated with the administration of quinidine the blood-pressure usually fell, but returned to its original level with the onset of normal rhythm or shortly afterwards. Carter, Dieuaide, and Burwell (12), however, report that in their series the average blood-pressure usually rose 30–40 mm. with the onset of normal rhythm. These workers also found that the vital capacity in patients was increased from 50 to 80 per cent. of the calculated normal. For periods up to a year the administration of quinidine in prophylactic doses does not seem to exert any effect on the blood-pressure. During the fall of blood-pressure associated with the administration of the drug faintness and visual symptoms have been not uncommon.

3. *Fluid output.* As in all cases of this series oedema and ascites had disappeared before quinidine was administered, much increase in urinary excretion was not to be expected. Nevertheless in several of the hospital cases in which this was recorded, a definite increase has been observed. No evidence has been forthcoming to show that the drug exerts any toxic action on the kidney.

VIII. *The Restoration of Normal Rhythm as a Therapeutic Procedure.*

The seventeen cases in Group A, Sub-group I, are all cases of auricular fibrillation of relatively short duration which had received no definite digitalis treatment before admission to hospital. With the exception of the three cases of exophthalmic goitre which will be reserved for special consideration, all these cases were admitted to hospital on account of failing compensation. In all these cases digitalis and rest in bed at least partially restored compensation, caused oedema and ascites to disappear, and reduced the ventricular rate below 80.

Normal rhythm was now restored and these patients were allowed up and discharged from hospital. All, with the single exception of Case XXXI, remained

as well up and about after the restoration of normal rhythm, as they had been resting in bed with fibrillating auricles and the corresponding ventricular rate controlled with digitalis.

In three out of these thirteen cases (II, IX, XXIX) objective signs of failure became less pronounced when normal rhythm was restored. There was also definite subjective clinical improvement. It was therefore concluded that in these cases cardiac efficiency had been raised to a higher level than under digitalis.

The majority of the remaining ten out of these thirteen cases experienced relief from subjective sensations in the chest, but signs and symptoms of failure being absent prior to the restoration of normal rhythm, no evidence of rise in cardiac efficiency could be adduced.

Of these thirteen cases, ten (II, XIII, IX, XI, XVII, XX, XXII, XXIX, XL, XXXVII) have returned to their normal lives, the women to their housework, one man to work on the tramcars, and one (XL), a hospital sister, to the work of her department. All these cases, with the exception of Case IX, had mitral stenosis. In all these ten cases it has been concluded that cardiac efficiency had been restored to its original level prior to the onset of auricular fibrillation, because the patient's capacity to do work without the onset of cardiac symptoms was now the same as before the known date of onset of fibrillation.

In the remaining three cases of the thirteen (XXV, XXX, XXXII) the approximate duration of fibrillation happened to be known, and although compensation was maintained, the exercise tolerance of these patients did not return to what it was before the onset of this event. These three cases had not got mitral stenosis. One had an adherent pericardium and mitral incompetence. The other two had no valvular lesions, but probably all three were rheumatic. In these cases we must suppose either that sudden lowering of myocardial efficiency occurred with the sudden onset of fibrillation or, what is more likely, that we are here dealing with cases of active myocardial disease.

In the one exception referred to (XXXI) the restoration of normal rhythm failed to maintain compensation, and though sino-auricular rhythm persisted with a normal pulse-rate, oedema and signs and symptoms of failure appeared. Whether this patient would have been any better under digitalis if fibrillation had been allowed to persist is extremely doubtful in view of the normal pulse-rate. It seems more probable that we are again dealing with a case of actively progressing myocardial disease. This patient had no valvular lesions.

Of the cases in this group, in two only (IX, XX) has relapse occurred. Case IX relapsed with signs and symptoms of failure. When Case XX relapsed no signs and symptoms of failure supervened, the ventricular rate did not rise, and she stated that she felt much better and had not felt so well or been able to do as much for eight years. A case such as this shakes one's faith in any conclusions drawn from clinical observations alone. The failure of the ventricular rate to rise might be attributed to a naturally acquired diminution of *a-v.* conduction or the same cause as the result of long-continued administration of quinidine. But at the same time it must be noted that the clinical improvement

in some of these cases has been very marked (Cases II, VIII, XVII, XX, XXXVII), and possibly more than can be attributed to the restoration of normal rhythm alone. Possessed with the obvious action of quinidine on cardiac rhythm, it would be only too easy to miss a possible action of the drug on the much more important function of cardiac muscle, contractility. Brody (23) has shown that quinidine diminishes the height of contraction of striped muscle. On the other hand, Cohn and Levy (24) state that quinidine during the fall of blood-pressure which is produced increases the amplitude of ventricular contractions. This effect is brought about by increased systolic contraction and not by increased diastolic relaxation. Boden and Neukirch (25) have shown that in the isolated perfused heart of the rabbit and human foetus quinidine dilates the coronary vessels. It must be remembered in this connexion that, although digitalis chiefly benefits cases of auricular fibrillation by diminishing *a.-v.* conduction, it exerts a definitely beneficial action on a certain number of hearts failing with normal rhythm. It will be interesting to test the action of quinidine on similar cases. Though no doubt quinine and quinidine act as cardiac depressants as far as cardiac excitability is concerned, the time-honoured but empirical administration of quinine tonics cannot be entirely ignored.

To sum up this section therefore: The value of restoration of normal rhythm in therapeutics is undoubted. In the absence of active progressive myocardial disease cardiac efficiency is restored to its original level before the onset of fibrillation. The most striking benefit is obtained in cases of mitral stenosis.

IX. *The Relative Value of Quinidine and Digitalis in the Treatment of Auricular Fibrillation.*

Group A, Sub-group II, includes eleven cases of auricular fibrillation, all of comparatively long duration. These cases had all received definite courses of digitalis prior to admission to hospital when normal rhythm was restored with quinidine. Whether digitalis treatment had been carried out effectively all the time fibrillation was present, is of course open to question. But all these cases, with two exceptions in which digitalis treatment was known to have been thorough, had at one time or another been admitted either to the London Hospital or the Heart Hospital. To eliminate this possible source of inaccuracy in the method, the patient's capacity to do work after the restoration of normal rhythm has been compared with what it was when he felt at his best during the known period of fibrillation.

With the exception of two cases (I, XLII) which were admitted to hospital compensated specifically for quinidine treatment, the remainder found their way into hospital on account of failing compensation. Accordingly, this group of cases probably represents that class of patients who do badly on out-patient digitalis treatment, and not the type of case which can be kept successfully compensated on digitalis for years.

In all these cases, however, digitalis has at least partially restored compensa-

tion at rest in bed, eliminated oedema and ascites, and reduced the ventricular rate below 80.

Of these eleven cases it has been concluded that in seven (I, IV, X, XXI, XXIV, XXVI, XXXVIII) the restoration of normal rhythm has maintained a higher level of cardiac efficiency than previously existed when fibrillation was present, the ventricular rate being controlled with digitalis. All these cases had mitral stenosis and incompetence, but the aortic valve was intact. Of these seven cases, in five (I, IV, XXIV, XXVI, XXXVIII) clinical improvement was striking, and the approximate date of fibrillation being known it was concluded that cardiac efficiency had been restored to its original level prior to the onset of auricular fibrillation. In the remaining two cases (X, XXI) clinical improvement was not very striking, and though they were definitely better than before treatment cardiac efficiency was not restored to its original level before the onset of fibrillation.

In two cases out of the eleven (III, VI) restoration of normal rhythm only maintained the same level of cardiac efficiency as digitalis. Case III had syphilitic aortitis with aortic incompetence and probably progressive myocardial disease. Case VI felt as well after discharge from hospital with auricular fibrillation while taking digitalis as after restoration of normal rhythm with quinidine. In the first instance he stopped taking digitalis and compensation failed within two months. But the second time, although he stopped taking quinidine, normal rhythm has now persisted for over a year, adequate compensation has been maintained, and he has returned to heavy work as a carman. This case brings out a practical point. In a large hospital out-patient department it will probably be easier to maintain normal rhythm with quinidine than to efficiently treat auricular fibrillation with digitalis. This patient had no valvular lesion.

In two cases out of the eleven (XIX, XLII) the patients were definitely worse after restoration of normal rhythm. Signs and symptoms of failure, previously absent, now appeared. Cardiac efficiency in these cases was definitely at a lower level with normal rhythm than with auricular fibrillation and the ventricular rate controlled with digitalis. Both these cases had mitral stenosis, and both developed tachycardia with the return of normal rhythm. The association of simple tachycardia with mitral stenosis, venous congestion, and decompensation is a common syndrome. The explanation of the tachycardia is uncertain. Tachycardia certainly cannot assist much in forcing blood through a stenosed mitral valve, and the frequent systoles of partially filled ventricles must waste much cardiac potential energy. The sudden onset of auricular fibrillation is almost invariably associated with an increase in the degree of pre-existing decompensation. But when the ventricular rate has been controlled with digitalis, such cases are occasionally better compensated than when normal rhythm was present with tachycardia. If we restore normal rhythm in such a patient, we go back to the unsatisfactory condition in which we have no possible method of controlling the ventricular rate. In removing the handicap of arrhythmia we have substituted the worse handicap of tachycardia. Unfortunately

the previous clinical histories of these two patients is not known, but it seems probable that they belong to this class, which is fortunately a comparatively small one. In these two cases quinidine has been discontinued, and to one digitalis has been readministered in the hope that relapse into auricular fibrillation will soon occur.³

To summarize this section: In the majority of cases the restoration of sino-auricular rhythm raises cardiac efficiency to a higher level than when auricular fibrillation was present, the ventricular rate being controlled with digitalis. In about half the cases the clinical improvement is striking, but in the other half not pronounced, and probably hardly worth the discomfort and risk associated with the treatment. The best therapeutic results are obtained in the presence of mitral stenosis and the absence of aortic incompetence. In a small minority of cases cardiac efficiency is definitely lowered by restoration of normal rhythm.

X. Quinidine in the Treatment of Auricular Fibrillation associated with Exophthalmic Goitre.

Four cases of auricular fibrillation associated with exophthalmic goitre have been treated with quinidine, and the results may be summarized as follows:

1. *Case XIII*, a female with exophthalmic goitre of five years' duration in whom the acute symptoms of the disease were subsiding. She also had slight aortic incompetence of rheumatic origin. She was admitted to hospital more on account of exhaustion and wasting than for reason of any definite cardiac symptoms. While the auricles were fibrillating, digitalis and bromide only succeeded in keeping the ventricular rate between 100 and 110, but after quinidine normal rhythm has persisted for nearly a year and the pulse-rate varies round about 90. The patient, however, remains practically bed-ridden on account of chronic rheumatism, and it is therefore impossible to form an opinion as to whether cardiac efficiency has been raised to a higher level than under digitalis or restored to its original level prior to the onset of auricular fibrillation.

2. *Case XVIII*, a female with exophthalmic goitre of one year's duration in the acute stage of the disease. While in hospital the restoration of normal rhythm controlled the ventricular rate far more effectively than digitalis. On discharge, however, simple tachycardia immediately supervened and signs and symptoms of failure, previously absent, now appeared. Restoration of normal rhythm therefore seemed to have definitely lowered the level of cardiac efficiency. After partial thyroidectomy, however (during the operation temporary relapse into fibrillation occurred), the patient returned to her normal life. Signs and symptoms of failure now remain absent, and normal rhythm with an average pulse-rate of 100 has dominated the heart for 200 days without relapse.

3. *Case XXXIX*, a female with exophthalmic goitre of six years' duration with the acute symptoms of the disease persisting. Digitalis reduced the ventricular rate to 90, but when normal rhythm was restored it rose to 110. Shortly

³ Of these two patients, Case XLII relapsed into fibrillation soon after quinidine had been discontinued, and the signs and symptoms of failure described above disappeared. In Case XIX normal rhythm has persisted in spite of digitalis.

afterwards relapse into auricular fibrillation occurred and digitalis failed to maintain compensation.

4. *Case XLV*, a male with exophthalmic goitre of ten years' duration in whom the acute symptoms of the disease had subsided. Restoration of normal rhythm maintained a lower ventricular rate than digitalis during fibrillation and at least the same level of cardiac efficiency. Relapse into fibrillation however, soon occurred.

This is an insufficient number of cases on which to base any conclusions. Nevertheless they are suggestive, and a short theoretical discussion of the subject seems worth while. The pathogenesis of exophthalmic goitre is still disputed. There are, however, two chief views possibly corresponding to two main groups of cases: 1. The toxic group with primary disturbance of thyroid function; 2. The nervous group with primary over-action of the sympathetic and secondary disturbance of thyroid action. In most cases of exophthalmic goitre digitalis is not very successful in controlling the ventricular rate. Whatever be the cause of tachycardia associated with this disease, whether it be due to increased katabolic rate or over-action of the sympathetic, if we restore normal rhythm we lose the only possible means we possess of controlling ventricular rate. Moreover, if the tachycardia of Graves's disease be due to over-action of the sympathetic, as by restoring normal rhythm we restore the control of the S.A. node over the ventricle we should therefore expect to increase the tachycardia. When discussing the restoration of normal rhythm in cases of mitral stenosis we saw that the handicap of tachycardia is probably greater than that of auricular fibrillation. It would therefore appear theoretically irrational to restore normal rhythm in cases of Graves's disease associated with auricular fibrillation during the acute stage of the disease. Cases XVIII and XXXIX suggest that this view is correct. There is, however, one possible exception. If we are contemplating thyroidectomy, it remains to be seen if the patient will stand it better with normal rhythm or with fibrillation. Unfortunately Case XVIII relapsed into fibrillation just before the operation, and therefore affords no evidence on this point. During the chronic stage of the disease (Cases XIII, XLV), and after thyroidectomy (Case XVIII), it would seem a rational procedure to restore normal rhythm both from theoretical considerations and the practical results that have been obtained.

XI. *The Prognosis and Tendency to Relapse in Successful Cases.*

All cases of this series have continued to take quinidine (gr. v twelve-hourly or eight-hourly according to the needs of each particular case) as a prophylactic against relapse with the exception of a few patients who will not bother to do so.

Of the twenty-eight successful cases in Group A which were discharged from hospital with normal rhythm, in seven only (IX, XX, III, IV, X, XXI, XXIV) has relapse hitherto occurred. In the remaining twenty-one normal rhythm has persisted up to date with a maximum duration of 382 days.

Of the twenty-one cases in which relapse has not yet occurred, three (II, VI, XVII) have not bothered to continue taking quinidine, but all the rest have taken the drug regularly.

Of the seven cases in which relapse has occurred, all took quinidine regularly, and normal rhythm persisted for periods varying from 338 days in Case IV to 40 days in Case VI.

Of the five successful cases which have been under observation for over a year, in three normal rhythm has persisted (I, II, VI), in spite of the fact that only one of them (II) took quinidine regularly. The remaining two of the five both took quinidine regularly, but Case III relapsed into fibrillation after 40 and Case IV after 338 days.

On the whole it may be stated that those cases in which relapse has occurred are patients with long histories of cardiac symptoms, with repeated attacks of failure, with large hearts, and with auricular fibrillation of long standing. With the exception of Case IX and possibly Case XLV, no patient with fibrillation of less than eight months' duration has hitherto relapsed into fibrillation.

Transient relapses have not been uncommon; for example, Case XIII. In Case XVIII relapse occurred when quinidine was discontinued prior to operation. Case I experienced four attacks of fibrillation when she first stopped taking quinidine, but since then, although she has omitted to continue taking the drug, no further relapse has as yet occurred. Case XL relapsed twice while taking quinidine gr. v twelve-hourly, but gr. v eight-hourly has successfully maintained normal rhythm.

Of the cases in Group B all with one exception relapsed into fibrillation while taking large doses of the drug. In Case V, however, relapse occurred after the drug had been discontinued on account of toxic symptoms.

The all-important question arises as to whether quinidine should be continued indefinitely after the successful restoration of normal rhythm as a prophylactic against relapse. The evidence so far obtained is conflicting, and no comparable statistical results can be obtained until all cases have either relapsed or died. At present there seems to be definite evidence to show that reduction of dosage or the discontinuation of the drug generally leads to relapse. But on the other hand, in a few cases the drug may be discontinued safely and no relapse into fibrillation occur, at least for quite long periods. In all cases, however, presumably a potential liability to relapse exists, seeing that the combination of factors which led to the inception of fibrillation might be expected to recur, and that the effect of quinidine on cardiac muscle wears off quickly. All other workers emphasize this tendency to relapse. Most have not continued giving the drug indefinitely, but those who have seem to agree that the tendency to relapse is reduced. It would therefore seem rational in the present stage of our knowledge to continue the prophylactic administration of the drug in all cases.

In his previous paper (1) the writer raised the point whether quinidine should be administered to patients suffering from conditions in which the incidence of fibrillation is exceptionally high—for example, rheumatic mitral stenosis and

Graves's disease—before the actual occurrence of this event. Lewis, however, points out that the combination of antagonistic factors leading to the production of circus movement is such that it does not follow that a drug which abolishes fibrillation in one case will prevent its occurrence in another. Moreover, even if quinidine were successful in this respect, possibly in some cases of mitral stenosis and in the acute stage of exophthalmic goitre, we wish to hasten rather than retard this event.

XII. *The Indications for Quinidine Therapy.*

Certain cases of auricular fibrillation are unsuitable for quinidine treatment. The selection of cases must always remain difficult, demanding as it does the careful consideration of a large number of different factors. These will be best considered systematically under the heading of the four main conclusions at which we have already arrived:

1. That quinidine will restore normal rhythm in 70–80 per cent. of cases of auricular fibrillation.

A successful physiological action of the drug in restoring normal rhythm is to be expected in patients who exhibit the following characteristics:

- (a) Cardiac symptoms of recent onset.
- (b) Auricular fibrillation of short duration.
- (c) Small hearts.
- (d) Active myocardial change in progress.
- (e) Middle age rather than youth.

2. Granted a successful physiological action of the drug a successful therapeutic result is to be expected in patients who exhibit the following characteristics:

- (a) Cardiac symptoms of short duration and auricular fibrillation of recent onset.
- (b) Rheumatic heart disease rather than cardio-vascular degeneration.
- (c) Stationary as opposed to progressive myocardial disease.
- (d) In the absence of progressive myocardial change when the onset of fibrillation has been synchronous with the first appearance of cardiac symptoms.
- (e) Mitral stenosis (with the exception of those in which the onset of fibrillation has been preceded by tachycardia and decompensation) rather than aortic incompetence or absence of valvular lesions.
- (f) Partially compensated cases in which digitalis has failed to control the ventricular rate, or compensated cases in which the ventricular action has remained very irregular though normal in rate.
- (g) Marked subjective symptoms of irregular heart action.
- (h) Cases of exophthalmic goitre in which the acute stage has subsided naturally or following thyroidectomy.

On the other hand, an unsuccessful therapeutic result may be expected if the following characteristics are present:

(a) Actively progressing myocardial disease, rheumatic, infective, syphilitic, or degenerative.

(b) Exophthalmic goitre during the acute stage of the disease.

(c) Mitral stenosis when tachycardia and decompensation immediately preceded the onset of fibrillation.

(d) When digitalis has controlled the ventricular rate without restoring compensation.

(e) Aortic incompetence.

(f) Varying degrees of heart-block.

3. That cases in which normal rhythm has been restored tend to relapse back into fibrillation.

The tendency to relapse is greatest in the cases which exhibit the following characteristics :

(a) Cardiac symptoms of long duration.

(b) Auricular fibrillation of long standing.

(c) Large hearts.

(d) Actively progressing myocardial disease.

4. That the administration of quinidine is attended with certain ill effects and even with considerable danger.

The following considerations have to be borne in mind :

(a) The toxic effect on the system generally is approximately proportional to the dosage. The consequent results are therefore to be expected in those cases in which a successful physiological action of the drug is not anticipated.

(b) The toxic effect of the drug on the myocardium is to be expected in cases of long-standing heart disease with large hearts and in cases in which digitalis, though successfully maintaining the ventricular rate, has failed to completely restore compensation.

(c) Embolism is to be expected in cases of auricular fibrillation of long standing, especially those in which previous attacks of decompensation have occurred, and presumably in patients who have previously shot emboli and are suffering from mitral stenosis.

Therefore in determining whether a given case is suitable for quinidine treatment, we have first to estimate the probability of obtaining a successful action of the drug, that is to say, restoration of sino-auricular rhythm. This procedure in itself is not necessarily therapeutic. If a successful physiological action of the drug seems probable, the possibility of producing a good therapeutic result must next be considered. Against this we have to set the likelihood of speedy relapse, in which case treatment is not worth while, and the possible dangers the patient incurs as the result of taking quinidine.

Fortunately the different factors controlling these four probabilities run concurrently as far as therapeutics is concerned. Thus in a patient with mitral stenosis, with auricular fibrillation of short duration, and with no previous attack of failure or embolic occurrences, a successful physiological action of the drug may be anticipated and a good therapeutic result expected, while the ill effects of

quinidine administration and relapse into fibrillation are both unlikely to occur.

On the other hand, in a case of mitral stenosis with a large heart, with cardiac symptoms of long standing and fibrillation of long duration, with previous attacks of failure and previous embolic occurrences, and in which digitalis has failed to restore compensation, a successful physiological action of the drug is not to be expected. Moreover, if it is obtained, a large dose of quinidine will be required, the toxic action of the drug on the heart and system generally will be severe, embolism is likely to take place, and relapse into fibrillation will probably soon occur.

In the present state of our knowledge it would therefore seem advisable to adopt the following provisional system of procedure :

1. In the absence of intercurrent disease and other contra-indications to give quinidine as a routine to all cases of auricular fibrillation of recent onset (one year or less), and especially to those with mitral stenosis, unless tachycardia and decompensation are known to have preceded the onset of fibrillation.

2. Not to give it to cases of auricular fibrillation of long standing (three years or more) which have received digitalis treatment and remain satisfactorily compensated under this form of therapy.

3. In cases of moderate duration (1-3 years) which are not doing very well on digitalis, the therapeutic possibilities of the treatment and the degree of risk incurred should be explained to the patient, who should make his own choice whether to undergo the treatment or not.

XIII. *Observations on Mitral Ventriculo-Diastolic Murmurs.*

In twenty-three out of the thirty-seven cases of this series mitral stenosis has been diagnosed. In thirteen of these mitral diastolic murmurs were present when the auricles were fibrillating. When normal rhythm was restored the mitral diastolic murmurs persisted and mitral presystolic murmurs appeared.

In two cases (III, XII) the mitral diastolic murmur persisted when normal rhythm was restored, but a presystolic murmur did not appear.

In two cases the diastolic murmur disappeared with the onset of normal rhythm and no presystolic murmur appeared. One of these cases (X) had aortic incompetence, and the other (XXVI) chronic high blood pressure.

In one case only (XXIV) no mitral murmurs were present while the auricles were fibrillating. When normal rhythm was restored a mitral diastolic but no presystolic murmur appeared.

In five cases (I, VII, XVII, I, XXI) no murmurs were present during fibrillation, but with restoration of normal rhythm both mitral diastolic and presystolic murmurs appeared.

Relapse into fibrillation has been invariably associated with the disappearance of presystolic and usually with the persistence of diastolic murmurs.

No further evidence has been obtained to support the view previously advanced (1) that aortic incompetence and chronic high blood pressure, by raising the diastolic intra-ventricular pressure, militate against the production of presystolic murmurs.

That the presystolic murmur is due to auricular systole and mitral stenosis is generally accepted, at least in this country. The observations recorded would support this belief, and are opposed to the conclusion of Reid (26), that the presystolic murmur is really ventriculo-systolic in time and due to regurgitation of blood through the mitral valve.

XIV. *Conclusion.*

In quinidine we have a drug which stands unique in therapeutics in that it produces the sudden disappearance of cardiac irregularity. This action of the drug is so obvious that in itself it constitutes a danger. The restoration of normal rhythm is not necessarily therapeutic. Normal rhythm is not necessarily the best method of working for every heart to adopt. In many cases the return to normal rhythm is associated with striking clinical improvement. In others there is little or none. A few are definitely worse when the normal action of the heart returns. Just as certain as it is that striking therapeutic successes may be obtained, it is equally sure that disastrous results may occur as the result of the treatment. By the judicious selection of cases on the lines indicated above, therapeutic successes may be raised to a maximum and the possibility of disasters reduced to a minimum. But some risk will always remain. Risks are repeatedly taken in surgery, and rightly. Every operation under general anaesthesia, however small, involves some risk. The writer believes that the therapeutic successes obtained with quinidine justify the risks incurred in the treatment of selected cases. Much responsibility must fall on the physician in the selection of cases. In the doubtful case the situation must be explained to the patient, who should be allowed to make his own decision.

The question of the quinidine treatment of extra-systoles, primary auricular flutter, paroxysmal auricular fibrillation, and auricular fibrillation associated with pregnancy has not been touched upon in this investigation. The possibility of quinidine causing foetal deaths or abortions in the latter connexion must be borne in mind. The writer hopes to take up this problem in the near future.

XV. *Summary.*

1. Forty-five unselected cases of auricular fibrillation under the age of 65 have been treated with quinidine, and in thirty-seven (82 per cent.) normal rhythm has been restored.

2. A standard system of dosage is described.

3. A thorough course of digitalis prior to quinidine treatment is advised, but the simultaneous administration of the two drugs is not recommended.

4. The ill effects of quinidine administration are discussed, but classified into (1) general, (2) embolic, (3) cardiac, (4) cerebral, (5) respiratory.

5. One case of sudden death attributable to quinidine treatment but not to embolism is reported.

6. Cardiac rhythm. In a few cases auricular flutter has preceded both the return of normal rhythm and relapse into fibrillation. Auricular extra-systoles have frequently occurred during the prophylactic administration of quinidine. There are no indication that relapse is imminent and therefore no indication that the dosage of the drug should be increased. Ventricular extra-systoles have been less frequent. Regular sequences of both varieties of these ectopic beats and one case of ventricular escape are described.

7. During quinidine the ventricular rate rises, but in cases which will be therapeutically successful drops to normal with the onset of normal rhythm. Following this event a transient bradycardia has been frequently observed. The blood-pressure falls during the tachycardia associated with quinidine administration but returns to its original level with the onset of sino-auricular rhythm.

8. In the absence of progressive myocardial disease the restoration of normal rhythm with quinidine restores cardiac efficiency and the pulse-rate to their original levels before the onset of auricular fibrillation.

9. In the majority of cases the restoration of normal rhythm with quinidine raises cardiac efficiency to a higher level than does the digitalis treatment of the same condition. In about half these the clinical improvement is striking, but in the remainder not pronounced. In the minority of cases the level of cardiac efficiency is reduced. These are probably cases of mitral stenosis in which tachycardia and decompensation have preceded the onset of fibrillation.

10. The quinidine treatment of auricular fibrillation is not advised during the acute stage of exophthalmic goitre. It may, however, be applied with beneficial results during the chronic stage of the disease or after thyroidectomy.

11. The best therapeutic results are obtained in rheumatic cases with mitral stenosis rather than in degenerative cases with aortic incompetence or without valvular lesions.

12. After the restoration of normal rhythm the prophylactic administration of quinidine has been continued indefinitely. Relapse has hitherto occurred in the minority of patients only, who were discharged from hospital with normal rhythm persisting.

13. Certain cases of auricular fibrillation are not suitable for quinidine treatment. In the selection of cases the probabilities of (a) restoring normal rhythm and of (b) producing a good therapeutic result must be balanced against (c) the probability of relapse occurring and (d) the risks associated with treatment. The indications for quinidine treatment are discussed in detail under these four headings.

14. Observations on mitral ventriculo-diastolic murmurs are recorded.

In conclusion the writer must again express his thanks to Dr. Charles Miller and the Physicians to the London Hospital who have allowed him to treat the cases in their wards. To Mr. Walton, who performed the operation, I am indebted for Case XVIII, and to Prof. Turnbull for the post-mortem findings in the two fatal cases.

The expenses of this research were defrayed by a grant from the Medical Research Council.

APPENDIX

Tables summarizing Results obtained and the Observations recorded in the 45 Cases treated.

EXPLANATION OF TABLES.

Aetiology.

- R. Rheumatism.
- D. Cardio-vascular degeneration.
- G. Exophthalmic goitre.
- S. Syphilis.
- O. Obesity.

Valvular lesions.

- MS. Mitral stenosis.
- MI. Mitral incompetence.
- AI. Aortic incompetence.

Mitral murmurs.

- PSM. Presystolic murmur.
- DM. Diastolic murmur.

Urinary excretion.

- + Increased.
- = Uninfluenced.
- Diminished.
- ? Unrecorded.

Cardiac efficiency after restoration of normal rhythm compared with that under digitalis treatment.

- + Increased.
- = Remained the same.
- Reduced.

Extra-systoles.

- A. Auricular.
- V. Ventricular.
- U. Undiagnosed.

Each vertical column under a particular case represents a separate course of quinidine treatment, and shows its nature and the results that ensued from it.

TABLE I (continued).

Case number	II	VIII	IX	XI	XIII	XVII	XVIII	XX	XXV	XXIX	XXX	XXXI	XXXII	XXXVII	XL	XLV
Number of days normal rhythm without relapse	382	317	—	300	293	225	202	—	44	144	110	107	80	83	115	—
Number of days normal rhythm before relapse occurred	—	—	72	—	—	—	—	113	—	—	—	—	—	—	—	27
Prophylactic dosage of quinidine in gr. per diem	10	10	10	10	10	nil	10	10	10	10	10	10	10	10	15	10
Relapse preceded by flutter	—	—	no	—	—	—	—	no	—	—	—	—	—	—	—	no

TABLE II. Successful Cases. Group A, Sub-group II.

Case number	I	III	IV	VI	X	XIX	XXI	XXIV	XXVI	XXXVIII	XLII
Age	58	36	40	37	30	42	58	39	52	32	30
Sex	F	M	F	F	F	F	M	F	F	M	F
Aetiology	R	RS	R	D	R	RS	R	RO	RD	R	R
Duration of cardiac symptoms in years	8	24	19	1	23	13	3	9	8	3	15
Duration of auricular fibrillation in months	32	24	24	6	14	2	8	48	18	9	?
Valvular lesions	MI	MI	MS	MI	MI	MS	MS	MI	MS	MI	MS
Distance of apex beat from mid-line in inches	4 $\frac{1}{2}$	4	5	4	5 $\frac{1}{2}$	4 $\frac{1}{2}$?	?	5	5 $\frac{1}{2}$	3 $\frac{1}{2}$
Number of days digitalis treatment before quinidine	760	nil	17	8	8	7	28	7	28	6	70
Total amount of quinidine administered in grains	95	150	315	375	288	40	153	465	120	162	55
Maximum dosage in grains six-hourly	5	10	10	10	12	5	7	15	16	11	5
Total number of days administered	6	6	18	15	10	3	7	13	2	7	3
Produced auricular flutter only	no	no	no	no	no	no	no	no	no	no	no
Produced normal rhythm preceded by flutter	yes	no	yes	yes	yes	yes	yes	no	no	yes	yes
Produced normal rhythm only	no	yes	no	yes	no	no	no	yes	yes	no	no
Prevention of embolism	no	no	no	no	no	no	no	no	no	no	no
Occurrence of embolism with onset of S.A. rhythm	yes	yes	no	no	?	no	no	no	no	no	no
Quinidine produced cerebral symptoms	no	no	no	no	no	no	no	yes	yes	no	no
Quinidine produced cardiac symptoms	no	no	no	no	no	no	yes	yes	yes	no	no
Mitral murmurs during fibrillation	nil	DM	DM	nil	DM	DM	nil	nil	DM	DM	DM
Mitral murmurs with return of S.A. rhythm	DM	DM	DM	nil	nil	PSM	PSM	—	nil	PSM	PSM
Urinary excretion	=	=	=	=	=	=	?	+	+	+	=
Cardiac efficiency compared with that under digitalis	yes	no	yes	yes	?	?	no	yes	yes	yes	no
Cardiac efficiency restored to level before onset of fibrillation	yes	no	yes	yes	?	?	no	yes	yes	yes	no
Extra-systoles	A	nil	A	U	AV	nil	nil	nil	nil	nil	A
Transient relapses	6	nil	nil	368	nil	190	1	nil	nil	nil	nil
Number of days normal rhythm without relapse	378	—	338	—	90	—	53	66	219	89	35
Number of days before relapse occurred	—	40	10	—	10	10	10	10	10	10	10
Prophylactic dosage of quinidine in grains per diem	nil	10	10	nil	no	no	no	no	no	no	no
Relapse preceded by auricular flutter	on one occasion	no	no	—	no	—	no	no	—	10	—

TABLE III. *Partially Successful Cases. Group B.*

Case number	V	XII	XV	XXIII	XXXV	XXXVI	XXXIX	XLIII
Age	35	26	47	63	38	57	43	44
Sex	F	M	F	M	F	M	F	M
Aetiology	R	RI	R	RD	R	RS	G	?
W.R. blood	-	-	-	-	-	-	-	-
Duration of cardiac symptoms in years	3	2	4	7	1	1	6	1
Duration of auricular fibrillation in months	?	?	26	48	MS	?	?	3
Valvular lesions	{ MS MI	MS MI AI	MI	MI	MI	MI	nil	nil
Distance of apex beat from mid-line in inches	4½	4	6½	?	5½	6½	3½	4½
Number of days digitalis treatment before quinidine	2	42	12	56	17	14	7	12
Total amount of quinidine in grains	387	15	144	253	200	200	162	392
Maximum dosage in grains six-hourly	10	5	7	11	10	10	9	14
Total number of days administered	18	5	10	9	8	7	9	12
Produced auricular flutter only	no	no	no	no	no	no	no	no
Produced normal rhythm preceded by flutter	no	no	no	no	no	no	no	no
Produced normal rhythm only	no	yes	yes	yes	yes	yes	yes	yes
Previous occurrence of embolism	no	yes	no	no	no	no	no	no
Embolism occurred with onset of S.A. rhythm	no	no	no	no	no	yes	no	no
Quinidine produced cerebral symptoms	no	no	yes	no	no	no	no	no
Quinidine produced cardiac symptoms	no	no	yes	yes	no	no	no	no
Mitral murmurs during fibrillation	DM	DM	nil	nil	DM	nil	nil	nil
Mitral murmurs with onset of S.A. rhythm	DM PSM	DM	nil	nil	DM PSM	nil	nil	nil
Urinary excretion	=	=	=	?	=	=	=	=
Cardiac efficiency compared with digitalis	?	?	?	-	+	?	?	+
Extra-systoles	nil	nil	nil	nil	U	nil	nil	nil
Transient relapses	nil	nil	1	8+	nil	nil	nil	3
Number of days normal rhythm before relapse occurred	3	3	1	1	3	3	12	56
Dosage in grains per diem when relapse occurred	nil	10	10	15	40	died	40	no
Relapse preceded by auricular flutter	nil	no	no	yes	no	no	no	no

* Total amount of quinidine all course included.

+ Relapse into auricular flutter.

TABLE IV. *Unsuccessful Cases. Group C.*

Case number	VII	XIV	XVI	XXVII	XXVIII	XXXIV	XLI	XLIV
Age	42	23	51	48	44	22	52	30
Sex	F	F	M	F	F	F	M	F
Aetiology	RO	R	D	R	R	R	O	R
W. R. blood	-	-	-	-	-	-	-	-
Duration of cardiac symptoms in years	1½	6½	3	6	12	7	2½	5
Duration of auricular fibrillation in months	12	3	?	48	84	6	6	?
Valvular lesions	{ MS MI	{ MS MI	nil	{ MS MI	MS MI	MS MI	nil	{ MS MI
Distance of apex beat from mid-line in inches	?	4½	?	5½	6	4½	6½	4¾
Number of days digitalis treatment before quinidine	nil	4	8	4	7	13	8	6
Total amount of quinidine in grains	450	862	666	180	392	300	378	364
Maximum dosage in grains six-hourly	7½	15	18	9	13	12	14	13
Total number of days administered	22	26	16	8	12	10	12	12
Produced auricular flutter only	no	no	no	no	no	no	no	no
Previous occurrence of embolism	no	no	no	no	no	no	no	no
Produced cerebral symptoms	no	yes	no	no	no	yes	no	no
Produced cardiac symptoms	yes	yes	yes	yes	yes	yes	yes	no
Urinary excretion	-	=	=	-	-	-	-	=

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VARIATIONS IN THE THRESHOLD IN RENAL GLYCOSURIA

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THE condition in which sugar is excreted in the urine, although there are no other signs of disease, is now well recognized. Originally described by Klemperer (1) in a case of renal disease, it was soon discovered that the condition occurred much more frequently when no signs of renal disease were present. At first isolated cases were reported, then small groups, and now large groups of cases (2-22). The condition cannot therefore be a rare one, for Leyton (22) has reported 18 cases, and the writer has seen 26 cases in all, including the 2 cases originally described by A. E. Garrod (6). H. Maclean (32) has also reported 23 cases, while John (33) has found that glycosuria occurred in the presence of normal blood-sugar in 99 cases. Moreover Folin has recently said that when he is teaching his class of students to test urines for sugar, he expects to find that one student out of every hundred will discover that he is passing sugar. The total number of cases is already over 200, and in spite of searching the literature, it is probable that some cases have been missed and many others not recorded.

The condition was fully described in this Journal (Graham (8)) in 1916, and it was pointed out that two types existed: the common one, in which less than 10 grm. of sugar a day were excreted, and another type in which 10 to 30 grm. of sugar were excreted. The case reported by Galambos (16) stands by itself at present, as over 100 grm. were excreted.

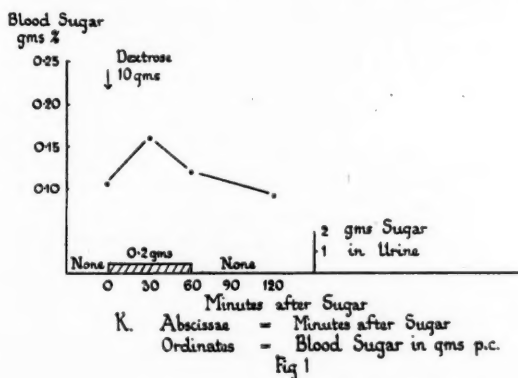
In this paper it is proposed to describe another type, and to discuss the light which it throws on the causation of the condition.

Two postulates have been laid down which are fulfilled in the great majority of the cases: (1) That the level of the blood-sugar before and after a carbohydrate meal shall not exceed the normal limits of variation; (2) That sugar shall always be present in the urine. The earlier cases reported by Garrod and Graham all fulfilled these two postulates, but in 1919 a patient was seen who did not appear to pass any sugar when the urine was tested with Benedict's solution after a day's fast, although he always passed appreciable amounts of sugar as soon as he ate anything at all. A second patient was seen in the same

year, who often did not pass enough sugar to be detected after a night's fast, but whose sugar tolerance was quite normal. Isolated cases of this condition have also been reported (Goto (9), Strouse (11), Murlin and Niles (15), Lothroh (19), John (33)), and in 1922 I have seen four more cases; while Goto and Nuno (20) found that 8 out of 53 healthy Japanese had a definite lowering of the threshold for sugar.

Since no sugar can be detected in the urine before meals, whereas it can be readily detected after a carbohydrate meal, the diagnosis of a mild diabetes of the type once called alimentary glycosuria seems at first sight to be justified. Yet the behaviour of the patients to the recognized tests for renal glycosuria is typical in all other respects.

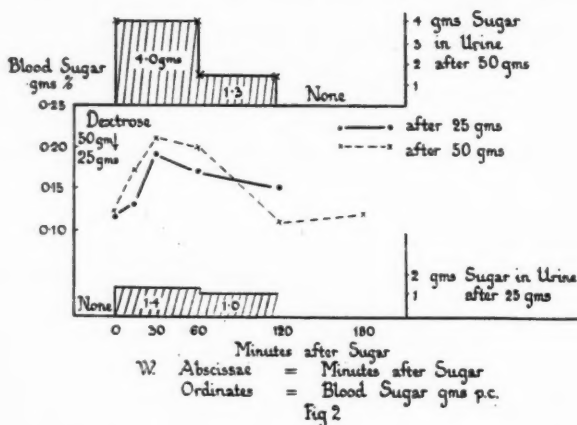
Case I. K., a boy aged 6 (24), who was first seen in January 1921. The father and mother were first cousins. An uncle had passed small amounts of sugar but had not been dieted strictly, and died of wounds during the war. A sister had passed sugar for a few weeks, but the sugar had disappeared on dieting. The patient had influenza at the age of four, and sugar was then discovered and had persisted in spite of dieting during the last two years. The amount of sugar was never large, and the highest percentage of sugar found in the urine was 0.9 per cent. The fasting value of the blood-sugar (Fig. 1) was



0.115 gm. per cent., and 30 minutes after a dose of 10 gm. of sugar the level of the blood-sugar had risen to 0.16 gm. per cent., but had fallen to 0.12 gm. after 60 minutes, and to 0.09 gm. after 120 minutes. No sugar could be detected in the urine with Benedict's solution before the sugar was given, but 0.2 gm. was excreted in the first hour after the sugar, and none in the second hour when the blood-sugar was falling from 0.12 gm. per cent. to 0.09 gm. per cent. No appreciable amount of sugar was excreted unless the level of the blood-sugar was over 0.12 gm. per cent., though it is not possible to say to what level the blood-sugar must rise before sugar is excreted in appreciable amounts. As I had not seen other cases of this kind in 1921 I hesitated to say that the boy had a renal glycosuria, since he only passed sugar after meals, although it was clear that the threshold was lower than usual. The boy was therefore given 1 oz. of bread at five meals in the day, and as no sugar could be detected in the urine the bread was increased to 2 oz. On this diet 2 gm. of sugar were excreted in the day. In the course of the next year sugar was very rarely detected, and he is now able to eat an ordinary diet without passing any sugar. The boy seems

quite well at present. In this case the lowering of the threshold seems to have been a temporary one, and resembles the case reported by Langdon Brown (25).

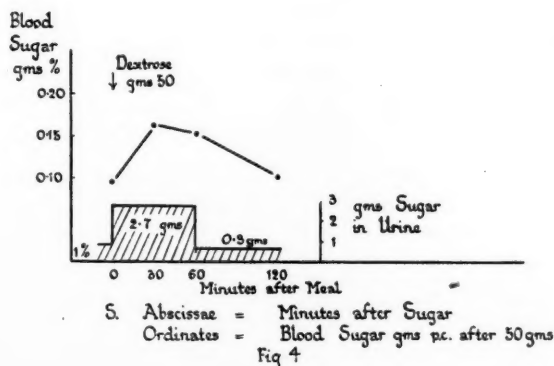
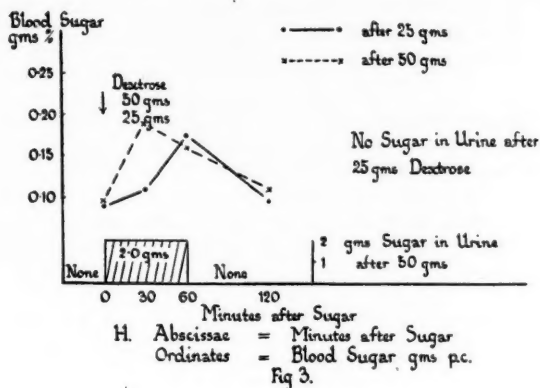
Case II. W., aged 53. The father had passed sugar for over forty years. One brother had passed sugar for eighteen years and still does so. His sisters have never been tested so far as is known. The patient had a bicycle accident at the age of 32, and sugar was then discovered in the urine. The patient was dieted to a certain extent, but always passed sugar. Four years later he was treated in Germany and ceased to pass sugar for a while, but during the next fourteen years he ate an ordinary diet and always passed sugar. In 1918 he had a heart attack, and as a result of the ill health which resulted, he was treated for diabetes mellitus on modern lines. It was found that if he ate a carbohydrate-free diet containing about 1,000 calories, 200 of which were supplied by alcohol, no sugar was excreted in the urine. If he exceeded this caloric value, sugar could always be detected in the urine. In April 1921 he consulted Dr. H. Morley Fletcher, who suspected that he had a renal glycosuria and sent him to me for examination. The fasting value for the blood-sugar (Fig. 2) was 0.115 gm. per cent., and



a dose of 25 gm. of sugar sent up the blood-sugar to 0.19 gm. per cent., but after 120 minutes the blood-sugar had only fallen to 0.15 gm. per cent. A dose of 50 gm. of sugar sent up the blood-sugar from 0.12 gm. per cent. to 0.21 gm. per cent. in 30 minutes, and after 60 minutes it had fallen to 0.20 gm. per cent. But 120 minutes after the sugar, the blood-sugar had fallen to 0.11 gm., and 180 minutes after the sugar it had risen slightly to 0.12 gm. The sugar tolerance as measured by the height to which the blood-sugar rises is slightly diminished. No sugar could be detected in the urine before the sugar was given in either experiment. After 25 gm., 1.4 gm. were excreted in the first hour and 1.0 gm. in the second hour. After 50 gm., 4.0 gm. were excreted in the first hour and 1.5 gm. in the second hour, but no sugar could be detected in the third hour. When carbohydrate was added to the diet, the amount of sugar which was excreted was very small.

Case III. O. H., aged 19. The family history is very interesting. The grandfather and grandmother were not related and, so far as is known, did not pass sugar. Of their five children, the mother, aunt, and uncle of this patient have all passed sugar for ten to fifteen years. They have all been treated as having diabetes mellitus, but have all gradually given up dieting as they did

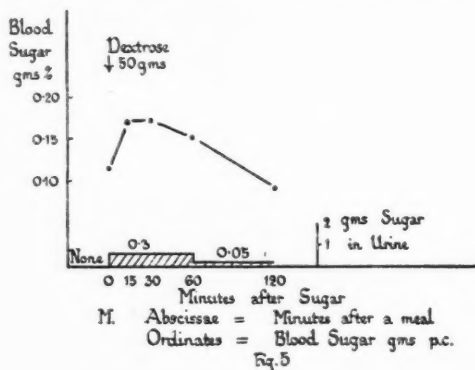
not feel well on the diet, and all feel very much better as a result. The patient has two brothers, one of whom passes sugar but is otherwise quite well. The uncle has six children, but none of them pass sugar. The aunt has two children who are both said to have passed sugar for a while. The patient had been over-working in the summer of 1921, and felt tired. He also complained of headaches. His mother suspected that he was suffering from diabetes mellitus, and asked his doctor to test the urine. This was done, and sugar was found. The patient was therefore treated as though he had diabetes mellitus, and fasted



until all the sugar disappeared from the urine. He continued to live on a carbohydrate-free diet as he passed sugar occasionally. His health did not improve, as he was still unable to read without having bad headaches, and was very easily tired. The first specimen of urine I examined some four months after the sugar had been discovered contained sugar and gave a very strong nitro-prusside reaction for aceto-acetic acid. The history of the discovery of the sugar and the family history, however, suggested that he had not got true diabetes mellitus, and the sugar tolerance was therefore tested. After 25 grm. of dextrose the blood-sugar rose (Fig. 3) from 0.095 grm. per cent. to 0.17 grm. per cent. after 60 minutes, and fell to 0.095 grm. per cent. after 120 minutes. No sugar could be detected in the urine by Benedict's solution either before or after the dose of sugar. After a dose of 50 grm. of sugar the blood-sugar rose from 0.095 grm. to 0.19 grm. per cent. in 30 minutes; fell to 0.16 grm. per cent. after 60 minutes,

and to 0.11 gm. per cent. in 120 minutes. During the first hour, 2.0 gm. of dextrose were excreted, but no sugar could be detected in the second hour. These curves are similar to those of other cases of renal glycosuria, and both the mother and uncle belong to the usual type, but pass sugar before the dextrose is given. The uncle's curve (Fig. 4) is given for comparison. After the blood-sugar tests, O. H. was given increasing amounts of bread, and when he ate 4 oz. of bread in addition to his ordinary diet he passed 3-4 gm. of sugar per day. I wanted him to keep on a diet containing only 2 oz. of bread, to see if the threshold would rise, as was the case in Case I, but when he found that he passed so little sugar he decided to follow his mother and uncle's plan and eat an ordinary diet. As soon as he did this he began to feel better and became capable of taking long walks. He has lost his headaches and feels quite different. He has gained 10 lb. in weight in two months.

Case IV. M., a physiology student, aged 23. Glycosuria was accidentally discovered as the result of taking a dose of sugar in order to determine the respiratory quotient for a class demonstration. The amount of sugar excreted was small, and no sugar could be detected the next day. He worked out his own blood-sugar curve, after a porridge and bread meal, and found that it lay well within the normal limits of variation. No sugar could be detected before the meal, but 1.16 gm. were excreted in the first hour and 0.2 gm.



in the second hour. His health was very good, but he had been worried to a certain extent by the knowledge of the glycosuria and also by the extra work he had done in determining his own curve. His renal functions had also been investigated, and the blood urea, urea concentration, phenolsulphone-phthalein, and chloride concentration tests were all quite normal. I repeated the experiment after a dose of 50 gm. of dextrose. The blood-sugar (Fig. 5) rose to 0.17 gm. after 15 minutes, and was still at this level at the end of 30 minutes; after 60 minutes it had fallen to 0.15 gm. per cent., and after 120 minutes to 0.09 gm. per cent. No sugar could be detected in the urine before the test, and only 0.3 gm. and 0.05 gm. of sugar were excreted in the first and second hours respectively. When Bang's method was used for estimating the amount of sugar in the urine, it was found that the fasting urine contained a reducing substance amounting to 0.15 gm. per cent., which is a very little higher than that of a normal person with this method.

The consideration of the results obtained on these patients shows that their sugar tolerance is quite normal, as the blood-sugar does not rise above normal limits after 25 and 50 gm. of sugar. The patients differ from the

members of the well-recognized types of renal glycosuria in that no sugar can be detected in the urine by Benedict's solution before the dose of sugar is given. Benedict stated that when eight drops of urine were added to 5 c.c. of solution and the mixture boiled for two minutes and allowed to cool five minutes, sugar could be detected in a concentration of 0.08 per cent. I have not found that the solution, as made up with English chemicals, is as delicate as this, but there is a slight change in the colour when sugar is present in a concentration of 0.15–0.2 gm. per cent. Therefore it is probable that the sugar was present in the urine of these patients in a concentration of less than 0.15–0.2 gm. per cent. Normal urine always contains small amounts of a reducing substance, and Pavy prepared an osazone from normal urine which was identical with that of dextrose. He thought that normal urine contained sugar in a concentration of 0.04 gm. per cent. Benedict and Osterberg (26) confirmed this, using a much more delicate method, and thought that sugar was present in a concentration of about 0.1 gm. They examined two individuals: one a healthy young adult who excreted about 0.5 gm. of sugar in the day, and the other a middle-aged man who excreted about 1 gm. in the day. When the urine of the latter was examined at short intervals after a meal, it was found that the concentration of sugar was quite considerable and could be detected with the ordinary Benedict's solution. Unfortunately no blood-sugar determinations are given in their paper, but it is possible that the elder of the two individuals belongs to the class of renal glycosuria which I have described in this paper.

Wallis and Bose (27), using another method, have also found that sugar is always present in the urine of healthy people. Folin and Bergrund (23), on the other hand, have recently stated that the reducing substance which is at present in the urine of healthy people is not dextrose, but is made up of small amounts of disaccharides like lactose and dextrin.

According to Benedict and Osterberg's view, there is no threshold for dextrose, since dextrose is always present in the urine, while on Folin's view—which is the older one—no sugar is excreted in the urine unless the blood-sugar rises above 0.17 gm. per cent. The actual point at which sugar appears in the urine differs according to various observers. I have found that no sugar can be detected in the urine by Benedict's solution in some healthy individuals until the blood-sugar rises above 0.19 gm. per cent., using Bang's method, which gives slightly higher figures than are obtained by other methods.

In the typical cases of renal glycosuria the threshold must be set at or below 0.10 gm. per cent., since sugar is excreted in appreciable amounts when the blood-sugar is at that figure. In Case I of this series the threshold is certainly above 0.115 gm. per cent., as no sugar was detected in the urine at that level. Although the blood-sugar was not detected above 0.16 gm. per cent., it is of course possible that it was above that level for a short time, so it is not possible to say at what level sugar was excreted. The period of time during which the level of the blood-sugar is above the threshold must be of importance in excretion of the sugar.

In Case II the threshold is above 0.12 gm. per cent., but there is again no evidence as to the exact level of the threshold.

In Case III the level of the threshold is higher, as no sugar was excreted, although the blood-sugar was detected at the level of 0.17 gm. per cent. and sugar was excreted when the level of the blood-sugar was detected at 0.19 gm. per cent.

In Case IV the threshold is above 0.115 gm. per cent. and is certainly less than 0.17 gm. per cent.

These observations show that the threshold may be set at very different levels, and that the cases described in this paper are intermediate links between the frank renal glycosuria cases and normal individuals. The amount of sugar excreted in these cases is very small, and it is possible that the amount of sugar which is excreted depends on the extent to which the threshold is lowered. If this is the case, then it is probable that the threshold in the cases which I described in 1916, where 30 gm. of sugar were excreted in the day, is very low.

It may be mentioned that several instances of a raised threshold are on record, and I have reported one case in which no sugar was excreted although the blood-sugar was 0.30 gm.

The name under which this condition is known has given rise to some controversy. Since the original patients all had definite signs of kidney disease, the name renal glycosuria seemed an obvious one. When it was discovered that sugar might be excreted in the urine, although no signs of kidney damage existed, the name of renal glycosuria seemed inapplicable. Salomon suggested the name diabetes innocens, and I have hitherto used this name. It has been pointed out, however, that however innocent the condition may be, it is certainly wrongly named diabetes from the derivation of the word, as there is no polyuria. Most observers have continued to use the name renal glycosuria, but Leyton (22) has raised objections to this name and has suggested the name negligible glycosuria.

There is some evidence to show that although there is no gross renal disease, yet the kidney plays a definite part in the condition. The threshold for various sugars in man is very different from that of dextrose: thus laevulose may be excreted in the urine after a dose of laevulose, although the blood-sugar does not rise above 0.14 gm. (Graham (28), Spence and Brett (26)), and lactose is excreted quantitatively when it is injected into the blood. These functions must, it would seem, be localized in the kidney.

Hamburger and Brinkman (30), working on the kidney of the frog, have found that by varying the amounts of calcium and potassium in the perfusing fluid and making the H-ion concentration the same as that of frog's blood, they have been able to show that dextrose is not excreted in the urine, whereas all the other sugars are. These experiments show that the threshold of the frog's kidney is different for the various sugars, and that it can be altered for dextrose by varying the physical characters of the perfusing fluid. So far there is no evidence that the physical characters of the blood play any part in altering the threshold, but it is an attractive hypothesis.

Hence, although the kidney may not be primarily at fault in these cases, yet it is intimately connected with the condition, and the name renal glycosuria seems to be the most appropriate that can be used.

Conclusions.

A new type of renal glycosuria is described, in which no sugar can be detected in the urine when the patient abstains from food for a short while, but in which sugar is excreted in the urine when carbohydrates are eaten.

The sugar tolerance, i. e. the height to which the level of the blood-sugar rises after a dose of sugar, is normal.

The patients form an important link between normal people and patients with a typical renal glucosuria.

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OBSERVATIONS WITH THE HAEMATOCRIT VOLUME-COLOUR INDEX

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Introduction.

THE object of this work was to determine within what limits the volume of the red cell varies in health and disease; and to establish a ratio, if this existed, between the volume of the red cell and its diameter.

By means of the haematocrit the red cells of the blood can be completely sedimented; this sediment is conveniently referred to as the red cell volume, and when expressed as a percentage of the whole blood is known as the haematocrit value.

An attempt was made, by determining the relation of the red cell volume to its content of haemoglobin in diseased states, to throw some light on the factors which influence the production and destruction of haemoglobin, and to determine in which diseased states the haemoglobin is deficient to a greater extent than the cell volume, a condition which must be effected either by red cell division, by deficient formation of haemoglobin, or by the action of a toxin on the circulating red cell, which results in its impoverishment in haemoglobin.

Definition of Haematocrit.

The haematocrit is an instrument used to record the corpuscular volume percentage of the blood. It consists of a haematocrit 'head' attached to a centrifuge machine. The haematocrit 'head' is a metal frame which holds two capillary tubes graduated conveniently into hundredths. The capillary tubes are filled with blood, and the blood is centrifugalized until the corpuscles are completely sedimented.

History of the Use of the Haematocrit.

Blix in 1885 originated the principle of this instrument. S. G. Hedin (1 and 2) in 1889 published the first paper on this subject. He used a hand-centrifuge with a speed of 8,000 revolutions per minute, and used Müller's fluid (sodium sulphate 1 part; potassium bichromate 2 parts; water 100 parts) in equal parts with blood to prevent clotting. Working with his own blood he obtained a constant haematocrit reading in from 5 to 7 minutes, namely 51.6.

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Daland (3) in 1891 found that a 2.5 per cent. bichromate solution gave the most accurate results. He centrifugalized at a rate of 10,000 revolutions per minute, and obtained a constant reading in 3-6 minutes. He found the average normal haematocrit value to be 51.8, the corresponding red cell count being 5,070,000 per c.mm.

Gaertner (4) and Friedheim (6) used bichromated blood for their observations and made an improvement in technique. Herz (7) in 1893 lined his capillary tubes with cod-liver oil to prevent clotting, and compared results with those readings obtained by the bichromate method. He found that the latter method gave results 14 per cent. lower than the former.

Koepe (8) in 1895 used 2.5 per cent. bichromate and blood in equal parts; he obtained figures similar to those of Hedin and Daland, finding the normal haematocrit reading to be 50.0. Koepe used cedar-wood oil to prevent clotting, and found nearly identical values with this method to those obtained by the bichromate method. Herz's bichromated blood values are probably all too low.

Capps (10) in 1903 used whole blood without the addition of any salt or other anticoagulant. He centrifugalized at a speed of 10,000 revolutions per minute for three minutes. He found the average normal haematocrit reading to be 51.5 for males and the corresponding red cell count to be 5,060,000. He measured the diameters of 100 red cells in each of his cases, and found the average normal cell diameter to be 7.6μ .

Kottmann (11) in 1905 used the haematocrit to determine blood-volume, by recording the difference in haematocrit readings before and after the injection of known quantities of isotonic saline.

Keith, Rowntree, and Geraghty (12) in 1915 made use of the haematocrit to determine total blood-volumes. They first determined the total plasma volume by means of their vital dye methods, and then used the haematocrit to find the proportion of corpuscles to the plasma; hence they calculated the total blood-volume. The normal haematocrit reading is given as 43.

Scott (13) in 1915 counted the red cells of the rabbit per cubic millimetre, and used the haematocrit to determine the total blood-volume of these cells. Subsequently he bled the rabbits and found that the volume of the red cells per million was less after bleeding than before; he found that the protein of the plasma was increased after bleeding, and concluded that the protein had left the corpuscles to enter the plasma.

Bleibtreu (5) in 1893 had attempted to find the plasma volume per cent. of the blood by estimating its nitrogen content before and after dilutions with magnesium sulphate solution; in view of Scott's findings this was an inaccurate method. Hamburger (34) made references to this work.

Epstein and Baehr (14) in 1916, using the haematocrit on cats' blood before and after pancreatectomy, found a decrease in the corpuscular content of the blood after operation, and deduced from this fact that an increase of plasma had taken place, and consequently an increase in total blood-volume, for they argued the red cells cannot vary in number in this short space of time.

Epstein (15) in 1916 used hirudin to prevent clotting, and cited a case of diabetes in which the haematocrit reading varied from 50 to 42.6 in the space of a few hours—that is to say, the plasma had increased from 50 to 57.4; again assuming that the corpuscles remained unchanged in number, Epstein argued that the total blood-volume had increased by $\frac{57.4}{50}$, that is, by 14.8 per cent.

Lindeman (16 and 17) in 1918 used the haematocrit to determine total blood-volumes. He based his calculations on the changes in corpuscular volume per cent. before and after the transfusion of a known quantity of blood whose corpuscular volume per cent. had been previously determined. This method is only applicable to anaemic bloods.

Cannon, Fraser, and Hooper (18) in 1917 used the haematocrit to determine the difference in the corpuscular content of venous and capillary blood in soldiers suffering from shock. They found that venous blood was more dilute than capillary. The corresponding red cell counts and haemoglobin values were in accord with these haematocrit findings.

Harvey (19) in 1919, using his own blood, found varying haematocrit values between 51.4 and 55.1. With citration of the same blood an average of 46.5 was found.

Gram (20) in 1921 used citrated venous blood and gave the limits of 41–51 as normal average haematocrit values in males and 36–45 in females.

Bock (22) and Denny (21) made use of the haematocrit for total blood determinations following on the lines of Keith and his co-workers.

To facilitate the interpretation of the relation between the haematocrit reading and the red cell count, and of the relation between haematocrit reading and the haemoglobin percentage, the following definitions are given:

Volume index. Capps introduced this term to embody the ratio of the haematocrit reading, expressed as a percentage of normal to the red cell count, expressed as a percentage of normal. Thus, where the haematocrit reading is 50.0, which is the normal reading, which is said to be 100 per cent., and where the red cell count is 5,000,000 per c.mm., which is a normal count, which is said to be 100 per cent., the volume index = $\frac{\text{haematocrit per cent.}}{\text{red cell count per cent.}} = \frac{100}{100} = 1$.

Herz had expressed this relation previously as 'das mittlere Volumen der einzelnen Zellen'; this would be represented in the above example thus:

$$\frac{50}{100} \times \frac{1}{5,000,000}, \text{ that is, } 0.000,000,1000 \text{ c.mm.}$$

For convenience, Herz referred to this as 1,000; and gave as the normal limits of the 'mean volume of a single cell' 800–1,000. In terms of Capps's volume index these figures are represented as 0.8–1.0; this is the more simple expression and has therefore been adopted in this paper.

Volume-Colour Index. This is a term used in this paper to express the relation between the red cell volume per unit of blood and its haemoglobin content, that is, the capacity of the cell volume for haemoglobin. If the haema-

toerit reading is 50.0, which is the normal haematocrit reading, which is said to be 100 per cent., and the haemoglobin is 100 per cent., then the

$$\text{Volume-Colour Index} = \frac{\text{haemoglobin percentage}}{\text{haematocrit percentage}} = \frac{100}{100} = 1.$$

Herz (7) had expressed this relation by the term 'Der spezifische Haemoglobingehalt'. He expressed the relation between the haemoglobin per cent. and the haematocrit reading so that in the above example 'der spezifische Haemoglobingehalt' would be $\frac{100}{50}$, that is, 2.0.

The technique used in this work for determining the cell counts, haemoglobin percentages, haematocrit readings, rate of red cell sedimentation, and measurement of red cell diameter are described in the following paragraphs.

(a) *Cell counts and haemoglobin values.* The red corpuscle counts were made with a Hawksley-Bürker double counting chamber, and an average of the two readings was taken, a hundred squares being counted.

The haemoglobin determinations were made by a Haldane's haemoglobino-meter.

(b) *Haematocrit.* The capillary tubes were filled with whole blood by aspiration from the finger, and the blood was centrifugalized for four minutes. The centrifuge used at first was a hand-turned instrument geared so that one turn of the handle turned the haematocrit head twenty times; by turning the handle 160 times per minute a speed of 3,200 revolutions to the minute was obtained.

The capillary tubes were cleaned with 1 per cent. acetic acid, followed by distilled water and absolute alcohol, and finally dried by ether.

In a series of thirty-four cases it was found that the haematocrit readings were mostly far higher than the red cell counts would lead one to expect in the light of the results of previous workers, and it was deduced that four minutes was not a sufficiently long period for the centrifugalizing of whole blood at the speed of 3,200 revolutions per minute; moreover, the physical work involved in turning the centrifuge handle 160 times per minute was too fatiguing for the writer to maintain longer than four minutes; therefore an electrical centrifuge was used with a speed of 3,600 revolutions per minute.

In a series of ten observations on the writer's blood an average haematocrit reading of 50 was obtained after twenty minutes' centrifugalizing; the highest reading being 52 and the lowest 49. This is a maximum deviation from the mean of 4 per cent. It was found that, when working with a speed of 3,600 revolutions per minute, normal blood must be centrifugalized for at least twenty minutes to sediment the corpuscles completely. Corresponding readings on the same blood where the hand-centrifuge was used gave higher haematocrit readings varying between 53 and 59 and were irregular. This hand-centrifuge clearly did not complete the sedimentation.

A further proof of this was afforded by a comparison of the haematocrit readings obtained by the hand-centrifuge and electrical centrifuge on the writer's blood, citrated and oxalated, using the paraffin block method, which will be

described later. In the case of citrated blood the hand-centrifuge gave an average reading of 54, the electric one of 44.6; and in the case of oxalated blood the hand-centrifuge gave a reading of 50, the electric one of 41.0.

Therefore a higher speed centrifuge made by Messrs. Baird and Tatlock was obtained. With this instrument one turn of the centrifuge handle revolved the haematocrit head sixty-five times; by turning the handle seventy times to the minute, a speed of 4,500 revolutions per minute was attained. A special haematocrit head was made for this instrument with a screw adjustment for holding the haematocrit tubes in position: the spring lever adjustment supplied was discarded in its favour, as blood not infrequently left the tubes with the latter arrangement. With this centrifuge it was found that normal whole blood was completely sedimented in from 5 to 10 minutes. Therefore, in making determinations on the blood in diseased states, either the electrical centrifuge was used for twenty minutes or this hand-centrifuge for from 5 to 10 minutes. The electrical centrifuge could not be used for ward cases, as at least five minutes of the pre-clotting phase of the blood was wasted in the transit of the blood from the ward to the laboratory. Citrated and oxalated blood were therefore used to see whether this difficulty could be overcome without introducing an error in technique.

For this purpose a paraffin block was obtained with six small craters. The craters were sprinkled over by the smallest amount of powdered crystals of sodium citrate that would adhere to the point of a needle; five drops of finger blood, obtained by a finger-prick, were collected in the crater, and mixed with the citrate crystals by aspiration into a glass tube drawn to a capillary. Potassium oxalate crystals were used in the same way for comparison. The blood was centrifugalized for twenty minutes in the electrical centrifuge.

In the case of the citrated blood an average of ten readings gave a haematocrit value of 44.6 with maximum deviation from the mean of 8.8 per cent. In the case of the oxalated blood an average reading of 41.0 with a maximum deviation from the mean of 16 per cent. With whole blood it was recorded above that an average haematocrit reading of 50 was obtained with a maximum deviation from the mean of only 4 per cent.

These experiments show that the oxalate reduces the red blood corpuscle volume to a larger extent than the citrate does, but both salts reduce the cell volume as compared with the whole blood method, the citrate by about 11 per cent. and the oxalate by about 19 per cent. The use of oxalate was therefore discarded.

However, in view of the fact that the maximum deviation from the mean in the case of citrated blood was 8.8 per cent., that is, double the maximum deviation encountered where whole blood was used, it was considered necessary to determine whether this was due to a source of inaccuracy having arisen from the fact that the citrate crystals were not weighed out in constant proportion to the blood in the paraffin block method, and so in some cases Gram's (20) technique was adopted, in which definite proportions of blood and citrate solution are used.

0.5 c.c. of a 3 per cent. solution of sodium citrate was drawn into a 5 c.c. syringe and venous blood allowed to fill the syringe after vein-puncture to 5 c.c.; the citrated blood was then centrifugalized, the haematocrit reading recorded, and multiplied by the factor $\frac{10}{9}$ to correct for the dilution of the blood by the citrate solution.

The haematocrit readings obtained by the whole blood method, using the hand-centrifuge for 5-10 minutes or the electrical centrifuge for twenty minutes; those obtained by the paraffin block method with citrate crystals, using the electrical centrifuge; and those obtained by the citrated venous blood method of Gram, using the electrical centrifuge, may be compared in Table I. In this table eight cases are shown on which all three of these methods were employed. The paraffin block method with citrate crystals and the citrated venous blood method of Gram may be further compared in Table II, in which nineteen cases are shown on which both these methods were employed.

Table I shows that the volume indices (Capps) where the whole blood method has been employed (A)—excluding the erratic case, No. 27—have an average of 0.96 and the greatest deviation from the mean is 4 per cent.; where the paraffin block method has been employed (B) the volume indices have a mean of 0.89 and the greatest deviation from the mean is 11 per cent.; where Gram's method has been employed (C) the average volume index is 0.80 and the greatest deviation from the mean is 14 per cent. Clearly the whole blood method gave the most accurate results, and both the citrated blood methods were inaccurate, but Gram's method is the more inaccurate of the two: this may be because the blood has been diluted, and, as will be shown below, the rate of sedimentation of the red cells is thereby increased; consequently a source of inaccuracy is introduced, or it may be due to an error in measuring the blood in a 5 c.c. syringe.

TABLE I.

Case No.	Method A. Whole Blood.			B. Blood citrated by Crystals on a Paraffin Block.			C. Citrated Venous Blood (Gram Technique).		
	Haemato-crit Values.	Red Cells per c.mm.	V. I.	Haemato-crit Values.	R. B. C. per c.mm.	V. I.	Haemato-crit Values.	R. B. C. per c.mm.	V. I.
2	45	4,616,000	0.98	43	4,616,000	0.93	43	5,387,000	0.81
13	52	5,280,000	0.98	45	5,280,000	0.85	43	5,692,000	0.75
14	40	4,112,000	0.97	41	4,112,000	0.97	41	4,644,000	0.73
23	42	4,296,000	0.98	42	4,296,000	0.98	35	3,682,000	0.94
26	27	2,840,000	0.98	24	2,840,000	0.91	22	3,075,000	0.70
27	27	5,184,000	0.52	26	5,184,000	0.50	33	4,613,000	0.72
29	47	5,064,000	0.94	42	5,064,000	0.84	45	5,111,000	0.88
31	46	5,096,000	0.92	40	5,096,000	0.78	43	5,431,000	0.79
Aver.	40.5	4,560,000	0.96	38.0	4,560,000	0.89	38.5	4,700,000	0.80

Table II shows that the average haematocrit reading where the paraffin block method (B) has been employed is 37.6, as compared with 37.7 where Gram's method (C) has been employed. The volume indices are 0.82 by both methods

and are about 14 per cent. too low; and it is to be emphasized that the use of citrate crystals in small indefinite proportions to the blood is less inaccurate than Gram's method, where the citrate was used in definite proportion to the blood. The citrate method gives constantly lower haematocrit values than the whole blood method by about 10-14 per cent.

The haematocrit readings obtained by the whole blood method, both in the case of normal blood and in the case of blood in diseased states, having been demonstrated to be more accurate than those obtained by either of the citrate methods, the whole blood method was finally adopted as alone being worthy of application.

TABLE II.

Case No.	Method B. Blood citrated by Crystals on a Paraffin Block.			Method C. Citrated Venous Blood (Gram).		
	Haemato-crit Values.	Red Cells per c.mm.	V. I.	Haemato-crit Values.	Red Cells per c.mm.	V. I.
1	38	4,944,000	0.77	49	4,690,000	1.05
2	43	4,616,000	0.93	43	5,387,000	0.83
4	50	5,056,000	1.0	54	5,602,000	0.96
5	45	4,952,000	0.92	41	5,100,000	0.80
6	39	4,600,000	0.84	40	4,160,000	0.95
7	32	4,688,000	0.69	32	4,853,000	0.67
7	37	5,288,000	0.71	32	4,888,000	0.66
7	32	4,648,000	0.70	30	4,588,000	0.65
7	40	5,120,000	0.78	39	5,111,000	0.76
9	42	4,952,000	0.85	41	4,640,000	0.89
11	19	2,460,000	0.76	17	2,487,000	0.68
11	18	2,496,000	0.75	18	2,452,000	0.75
12	40	4,312,000	0.93	38	4,850,000	0.70
15	39	5,128,000	0.76	41	4,888,000	0.85
16	60	7,496,000	0.80	62	6,667,000	0.94
18	20	2,444,000	0.82	18	2,475,000	0.72
19	45	5,048,000	0.90	42	5,600,000	0.75
21	42	4,848,000	0.85	42	4,747,000	0.89
22	35	4,004,000	0.87	38	3,609,000	1.06
Aver.	37.6	4,584,000	0.82	37.7	4,567,000	0.82

Wright (31) recorded the minimum amount of oxalate of sodium in blood which is required to prevent coagulation to be between 1 in 400 and 1 in 900. Campbell (32) in a recent paper used oxalate crystals and venous blood in the proportion of 1 in 200 and recorded a haematocrit value of 40 as normal. Falta and Richter-Quittner (33), using 1 in 33 oxalated blood, found a haematocrit value of 40; using 1 in 100 they found a haematocrit value of 42, while using whole blood and hirudinized blood values of 43 were obtained in the case of each. Keith, Rowntree, and Geraghty (12), using sufficient oxalate crystals to prevent coagulation, give 43 as the normal haematocrit value. Harvey (19), using 1 in 75 sodium citrated blood, found an average haematocrit value of 46.8, compared with 53.25 using whole blood. In Gram's method, which was used in the present work, the proportion of citrate to blood is 1 in 333.

There is then a general agreement, where oxalate and citrate have been used in proportions from 1 in 75 to 1 in 333, that the normal haematocrit value lies

between 40 and 43, whereas Capps, using whole blood, found it to be about 48; and in this work, using whole blood, the normal average haematocrit reading was found to be 50.0. It was not determined whether the lower haematocrit values obtained by citrate and oxalate as compared with whole blood determinations were due to the production of a hypertonic plasma or some other cause.

(c) *Sedimentation.* The rapidity with which the red cells sediment varies in health and disease, and consequently the time which the red cells take to sediment completely varies. Whole blood is sedimented less readily than salted blood. In pregnancy and in diseased states, such as nephritis and septicaemia, the blood sediments rapidly, as also in anaemic states, whereas in such conditions as polycythaemia the blood sediments slowly.

The rate of sedimentation must therefore be considered in any conclusions based on haematocrit readings or on cell counts.

An index of the sedimenting rate of the salted blood may be taken by allowing corpuscles to settle in a 10 c.c. measuring cylinder divided into hundredths, and recording the height of the column of red cells from time to time. A constant reading was not attained for about twenty-four hours with normal blood, though in certain diseased states it was attained within an hour.

(d) *Cell diameters.* The cell diameters of eighty perfectly round cells were recorded and an average taken. The diameters were measured by means of an eye-piece micrometer, a Zeiss E objective, and an eye-piece magnification of X 20. With a tube length of 45 cm. each division of the eye-piece micrometer measured 1 micron or μ . By this means the diameters of the cells could be accurately gauged to 0.25 μ . The cells were measured both in the counting chamber in Toisson's fluid and in a dry unfixed film. Of the two methods it was found that fewer variations in shape and a greater number of perfectly round cells were encountered in the wet than in the dry preparation. It was found that the corpuscles of the writer's blood had an average diameter of 8.4 when measured in Toisson's fluid and 8.6 when measured on a dry film, 300 cells being measured in each case.

In the ten cases of blood in diseased states on which both methods were performed the dry preparation tended to give a measurement greater than the wet by about 0.4.

Discussion of Results obtained.

Volume-Colour Indices (that is, $\frac{\text{haemoglobin per cent.}}{\text{haematocrit per cent.}}$). In Table III it is noticeable that in those cases in which the whole blood method (A) has been performed, twenty-one of the twenty-six cases recorded show Volume-Colour Indices which are within the limits of 0.90 to 1.00. These limits may therefore be regarded as the normal limits. The five abnormal cases are No. 43, a woman with Banti's disease, who has a Volume-Colour Index of 0.75; No. 8, a patient near death from pernicious anaemia, with a Volume-Colour Index of 0.81 and

TABLE III.

In this table are given whole blood haematocrit readings in diseased states with corresponding cell counts, haemoglobin percentages, and measurements of cell diameters.

Case No.	Diagnosis, Date, and Method.	Haemato- crit Reading.	Haemo- globin %.	Red Cells per c.mm.	Vol.- Colour Index.	Colour Index.	Vol. Index.	Aver. Diam. in Microns Red Cells.	
								Dry.	Wet.
G. G.	Normal								
	26.1.22 A	50	94	5,368,000	0.94	0.89	0.94	—	—
	26.1.22 A	50	94	5,488,000	0.94	0.87	0.93	—	—
G. H. R.	3.1.22 A	53	96	5,296,000	0.91	0.91	1.00	8.6	8.4
								av. 300 cells	
2	Malaria								
	29.11.21 A	45	90	4,616,000	1.00	0.98	0.95	—	—
8	Pernicious anaemia								
	<i>Died 29.1.22</i>								
	5.1.22 A	16	26	1,072,000	0.81	1.21	1.49	7.6*	—
	23.1.22 A	17	21	900,000	0.62	1.17	1.88	—	—
13	Malaria								
	25.11.21 A	52	90	5,280,000	0.86	0.85	0.98	8.6	—
14	Malaria								
	28.11.21 A	41	75	4,112,000	0.93	0.91	0.97	—	—
20	Empyema chronic								
	10.30 a.m. 27.1.22 A	32	72	4,400,000	1.13	0.82	0.73	—	8.3
	2.0 p.m. 27.1.22 A	34	76	4,592,000	1.09	0.84	0.75	—	7.8
23	Leprosy								
	2.1.22 A	42	82	4,296,000	0.98	0.95	0.98	8.0	—
24	Chlorosis (masked)								
	14.1.22 A	36	88	4,336,000	1.22	1.04	0.82	7.9	5.8
26	Tabes dorsalis								
	<i>Died 12.1.22</i>								
	9.1.22 A	27	53	2,840,000	0.98	0.94	0.98	8.1	—
27	Malignant endocarditis								
	<i>Died 11.1.22</i>								
	9.1.22 A	27	58	5,184,000	1.07	0.56	0.52	8.2	—
29	Convalescent influenza								
	13.1.22 A	47	90	5,064,000	0.95	0.90	0.94	8.3	—
30	Graves's disease and chronic nephritis	A	32	62	4,576,000	0.97	0.69	0.71	8.1
31	Dyspepsia								
	20.1.22 A	46	98	5,096,000	1.13	0.98	0.92	7.7	—
33	Dyspeptic anaemia								
	29.1.22 A	37	60	4,160,000	0.81	0.72	0.88	—	7.8
34	Diabetes								
	30.1.22 A	44	86	4,520,000	0.88	0.95	0.98	—	8.1
	3.2.22 A	42	80	4,224,000	0.95	0.95	1.0	—	8.1
	6.2.22 A	41	86	4,592,000	1.05	0.84	0.91	7.8	7.9
35	T. B. broncho- pneumonia	A	40	80	4,688,000	1.00	0.87	0.87	—
36	Mitral stenosis, marked cyanosis								
	2.2.22 A	60	102	6,200,000	0.85	0.82	0.96	—	8.4
37	Aortic re- gurgitation								
	3.2.22 A	47	68	5,544,000	0.72	0.62	0.85	8.2	7.8

* Variants 14.2–6.6 μ .

TABLE III (continued).

Case No.	Diagnosis, Date, and Method.	Haemato- crit Reading.	Haemo- globin %.	Red Cells per c.mm.	Vol.- Colour Index.	Colour Index.	Vol. Index.	Aver. Diam. in Microns Red Cells.	
								Dry.	Wet.
38	Thrombo-angiitis obliterans (Leo Buerger) 7.2.22 10.30 a.m. A 9.2.22 12.0 a.m. A	57 52	106 100	5,896,000 5,264,000	0.93 0.96	0.91 0.96	0.96 1.00	—	—
39	Congenital pul- monary stenosis 10.2.22 A	79	130	8,184,000	0.82	0.80	0.96	7.6	7.1
40	Catarrhal jaundice 13.2.22 A	41	80	4,816,000	0.98	0.83	0.85	8.6	8.4
41	Bronchitis, dyspnoea 14.2.22 A	41	78	4,488,000	0.95	0.87	0.91	8.9	7.8
42	Haematuria, spastic para- plegia 16.2.22 A	39	74	4,408,000	0.94	0.84	0.89	—	7.9
43	Banti's disease A	20	30	2,660,000	0.75	0.54	0.77	7.9	7.5
44	Cardiac dyspnoea A	45	80	4,480,000	0.88	0.88	1.00	8.3	7.9
7*	Acute nephritis 10.11.21 B C 17.11.21 B C 5.12.21 B C	37 32 32 30 40 39	68 — 82 — 80 —	5,288,000 4,888,000 4,648,000 4,588,000 5,120,000 5,110,000	0.91 — 1.28 — 1.00 —	0.65 — 0.90 — 0.78 —	0.71 0.66 0.70 0.65 0.78 0.76	8.2 — 8.3 — 7.9 —	— — — — 7.5 —
11*	Anaemia, secondary 24.11.22 B C 6.12.22 B C	19 17 18 18	24 — 25 —	2,460,000 2,487,000 2,496,000 2,452,000	0.63 — 0.69 —	0.41 — 0.50 —	0.76 0.68 0.75 0.75	— — 7.7 —	— — 7.3 —
12*	Acute influenza, septicaemic type 23.11.21 B Died 24.11.21 C	40 38	84 —	4,312,000 4,850,000	1.05 —	0.98 —	0.93 0.70	7.9 —	— —
18*	Subacute nephritis 12.12.21 B Died 13.12.21 C	20 18	38 —	2,444,000 2,475,000	0.95 —	0.79 —	0.82 0.72	7.4 —	— —

* These cases have been placed at the end of Table III, because method 'A' (the whole blood method) was not performed in these cases.

Method 'B' is the citrate crystal paraffin block method.

Method 'C' is the citrated venous blood method of Gram.

later of 0.62; No. 37, a man who had aortic regurgitation, with a Volume-Colour Index of 0.72; and No. 11, a patient suffering from a severe secondary anaemia, who presented a Volume-Colour Index of 0.63. Citrate was used on this case, but had whole blood been used, an even lower Volume-Colour Index would have been obtained, owing to the tendency which citrate has of reducing the haematocrit value and so raising the Volume-Colour Index.

The fifth abnormal case is No. 22, a woman who had recovered from chlorosis, who showed a Volume-Colour Index of 1.22, that is, 22 per cent. above unity; this may be due to the haematocrit reading being too low owing to the escape of some

of the column of the red cells from the peripheral end of the capillary tube. On the other hand, incomplete sedimentation of the red cells, by producing a haematocrit reading which is too high, will occasion a Volume-Colour Index which is too low.

Capps did not relate the haemoglobin to the cell volume per cent., but from his data in a series of thirty cases of pernicious anaemia an average Volume-Colour Index as high as 0.90 was calculated. In one case with the cell volume as low as 16 per cent. of the normal, that is, a haematocrit reading of 8.0, the Volume-Colour Index was found to be 0.96.

In this work only one case of pernicious anaemia was observed. In this case a low Volume-Colour Index, 0.81, was found three weeks before death took place, and as low as 0.61 six days before death.

A low Volume-Colour Index is a rare occurrence in pernicious anaemia, but in view of the case recorded in this paper it would seem that the haemoglobin does become destroyed in excess of the cell volume as death approaches.

It would be of interest to determine whether in pernicious anaemia, during recovery from a relapse, the haemoglobin is restored at the same rate as the cell volume, or whether there is a lagging of haemoglobin regeneration behind cell volume regeneration for about six weeks, as is found where haemorrhage has taken place.

From Capps's data in a series of thirty-five cases of secondary anaemia an average Volume-Colour Index of 0.85 is calculated; however, in the two cases of cancer in this series the low Volume-Colour Indices of 0.58 and 0.78 are found, showing a destruction of haemoglobin in excess of cell volume to a marked degree; or, expressed otherwise, a failure of production of haemoglobin to a more marked degree than of cell volume. Capps's figures for acute septic anaemia yield normal Volume-Colour Indices; however, in a series of nine cases of severe chlorosis the low average Volume-Colour Index of 0.69 is found. Campbell (32), in a recent communication, found that the 'Haemoglobin Index'—which is the Volume-Colour Index of this paper—is a very constant quantity; however, it may be noted that the Haemoglobin Index is as low as 0.65 in the case of cancer which he publishes; with both of these conclusions the results of the writer are in agreement.

In cases of severe septic anaemia Capps found that the red cells were smaller than normal. In this connexion, Cannon, Fraser, and Hooper (18) publish an instructive case which is apparently an exception to this, a patient with a severe wound of the buttock, who died of septicaemia on the eighth day, labelled 'progressive dilution of the red blood cells'. Unfortunately, haematocrit readings were not made in this case. The colour index, however, shows that the haemoglobin diminishes to a greater extent than the red cells from the first to the third day, the colour index being 0.81-0.73-0.69, but that from the third day to the eighth, when death took place, the colour index gradually rose from 0.69 to 1.25; the red cells had fallen from 5,400,000 to 2,000,000 per c.mm. and the haemoglobin from 85 per cent. to 50 per cent. In this case it seems probable that the high

colour index is due to the fact that the cells contain a larger quantity of protoplasm than normal cells and consequently a high content of haemoglobin.

It may be concluded that the normal limits of the Volume-Colour Index lie between 0.90 and 1.00. There is no evidence that in any condition a Volume-Colour Index of higher degree than 1.0 exists; where it is found it is due to too low a haematocrit value from escape of some of the column of red cells from the capillary tube. In this work a low Volume-Colour Index was found in four out of the twenty-six bloods examined: in a man who had severe secondary anaemia, in whom post-mortem revealed no primary cause except piles, in a woman with pernicious anaemia in the terminal stages, in a woman suffering from Banti's disease, and in a patient who had aortic regurgitation.

It is claimed that the Volume-Colour Index gives more information than the colour index in regard to the content of haemoglobin in the red cell. The colour index is an index of haemoglobin per individual red cell: the Volume-Colour Index is an index of haemoglobin per unit volume of red cell protoplasm. A low colour index signifies a cell which contains a lesser quantity of haemoglobin than the normal cell, but the haemoglobin per unit volume of protoplasm may be normal as the cell itself might be smaller than normal. A low Volume-Colour Index, however, definitely stands for a red cell protoplasm which is poorer in haemoglobin than normal.

In the same way a high colour index signifies a cell which contains more haemoglobin than the normal cell; but the haemoglobin per unit volume of red cell protoplasm, far from being above normal, is often normal and sometimes even lower than normal.

Also wherever the cell count is inaccurate, as it tends to be in rapidly sedimenting bloods, the Volume-Colour Index is a more accurate index than is the colour index.

Volume indices (that is, $\frac{\text{haematocrit per cent.}}{\text{red cell count per cent.}}$). The volume indices in Table III, with the exception of five cases, all lie within the limits 0.90 and 1.00, which may be regarded as the limits of health.

In No. 8, a woman suffering from pernicious anaemia, the volume index is 1.49 on 5.1.22 and 1.88 on 23.1.22; this high volume index is characteristic of pernicious anaemia and is in accordance with Capps's findings.

In No. 24, a woman who had had chlorosis, a volume index of 0.82 is met. In view of the Volume-Colour Index in this case being 1.22, it is probable that the haematocrit reading was too low; however, Capps found a true low volume index in chlorosis of severe type.

In No. 27, a man suffering from malignant endocarditis, the very low volume index 0.52 was found; this low value may be in part accounted for by the fact that the cell count is too high, and it is suggested that too high a cell count may be obtained in bloods which sediment rapidly, which was the case in this instance.

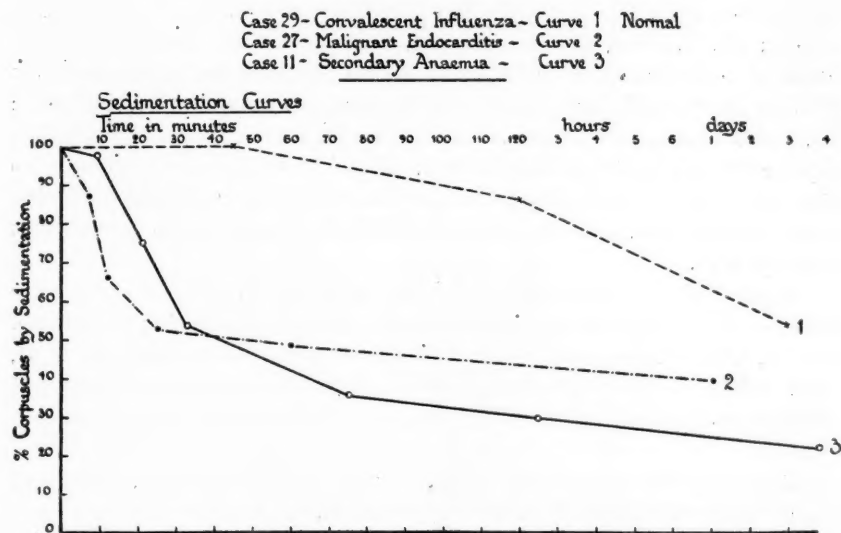
No. 30, a woman who suffered from Graves's disease and nephritis, shows a low volume index, 0.71; No. 20, a man suffering from chronic empyema,

also shows a low volume index, 0.73. The blood in these two cases also sedimented rapidly, and the low volume index is no doubt partly due to the high cell count which may result.

It may be concluded that the normal limits of the volume index lie between 0.90 and 1.00. A low volume index is unusual. Too high a cell count seems to account for many of the apparently low volume indices.

Capps found a low volume index in severe chlorosis and in septic anaemias.

In this work a high volume index was found in pernicious anaemia, which is in accordance with Capps's findings.



Sedimentation of corpuscles. Sedimentation curves of twenty-six venous bloods were plotted. Three of these curves are produced. Curve 1, from a case of convalescent influenza, is given as an example of a normal curve and is representative of twelve normal curves. Curve 2, from a case of malignant endocarditis, and Curve 3, from a case of severe secondary anaemia, are given as examples of a rapidly sedimenting blood and are representative of eight cases who present steep sediment curves, similar to those shown by these two curves. These eight cases which showed steep curves were No. 7, a woman with acute nephritis; No. 11, a man affected with a severe secondary anaemia; No. 8, suffering from pernicious anaemia; No. 12, from acute influenza of the septicaemic type; No. 18, from diffuse nephritis; No. 20, from chronic empyema; No. 26, from tabes; and No. 27, from malignant endocarditis.

The usual method of diluting the blood 200 times with Toisson's fluid for making the cell count, in spite of the usual shaking of the corpuscles in the diluting pipette and the discarding of the first drop, cannot be an accurate method of cell counting where a rapidly sedimenting blood is being examined. For

example, Case 12, of acute influenza of the septicaemic type, attained within sixty minutes that degree of sedimentation which a normal blood attains in twenty-four hours or more. When such a blood is further diluted 100 or 200 times in the diluting chamber, the rapidity of red cell sedimentation is further increased, and it is suggested that the cell counts must tend to become too high on this account, the cells having fallen by gravity to the lowest end of the pipette; the high cell count results in a low volume index.

It will be seen that in all the eight cases which show rapidly sedimenting bloods the volume indices are low, with the exception of the case of pernicious anaemia. No. 7, a woman affected by acute nephritis, has a volume index of 0.66; No. 11, a man with severe secondary anaemia, has a volume index of 0.70; No. 12, a man who had influenza of the septicaemia type, has a volume index of 0.70; No. 18, a patient with diffuse nephritis, has a volume index of 0.72; No. 20, suffering from chronic empyema, has a volume index of 0.72; No. 26, from tabes, has a volume index of 0.75; No. 27, a patient with malignant endocarditis, has a volume index of 0.72. It is claimed that the cell count is too high in these cases, and that the low volume index is not due to the red cells being some 25-30 per cent. lower in volume than normal red cells, but to the cell count being too high.

The rapidity of sedimentation does not vary directly with the corpuscular content of the blood nor with its richness or poorness in haemoglobin; for instance, Case 12, with a haematocrit value of 38 and a haemoglobin percentage of 84, has a rapid rate of sedimentation. Cases 7 and 27 also yielded blood which had a rapid rate of sedimentation and whose red cell volume was only moderately reduced.

It is interesting to note that death took place in Cases 8, 11, 12, 18, 26, and 27 shortly after the sediment curves were recorded.

Biernacki (25), Abderhalden (26), Linzenmeier (27 and 30), Vorschütz, J. (28), Fähræus (29) have made experiments on the sedimentation of the red corpuscles.

The observations in the present work suggest that in certain cases, especially near death and in cases of bacterial blood infection, entirely erroneous red cell counts may be obtained due to rapid sedimentation; any conclusions based on cell counts in such cases are therefore inaccurate.

Haematocrit readings, however, are not subject to this error. The blood is drawn straight into the capillary tubes and there is no preliminary dilution of the blood in the diluting pipette as is undertaken in red cell counts.

Cell diameters. The average normal cell diameter was found to lie between $7.6\ \mu$ and $8.4\ \mu$ when measured in Toisson's fluid, and between $8.0\ \mu$ and $8.8\ \mu$ measured in the dry film. No constant correspondence between the volume indices and the average diameter of the red cell was detected. This is only to be expected when it is considered that a cell may increase or diminish in volume quite independently of its diameter. As an example of this, No. 39, a case of congenital pulmonary stenosis, may be cited. This case had consistently low cell diameters, $7.1\ \mu$ - $7.6\ \mu$, when examined both in dry and wet films, whereas the

volume index is a normal one, 0.96. It may be argued that the haematocrit value of 79 in this case was too high, and that 10-15 minutes' centrifugalization at 4,600 revolutions is not sufficient completely to sediment a viscous blood such as was found in this case.

In Case 8, of pernicious anaemia, the average diameter was $9.8\ \mu$ on 15.11.21, and $7.6\ \mu$ on 5.1.22, with variants from 14.2 to $5.5\ \mu$.

It is to be noted that the cases which had a low volume index and rapid sedimenting rate all had normal cell diameters, which is a further argument in support of the contention that the cell counts were too high.

Capps (10) found a close correspondence between measurements of the cell diameters and the volume indices, except in pernicious anaemia where anisocytosis was marked.

Any difference between the osmotic pressure exerted by Toisson's fluid and that exerted by the plasma of the blood observed is a source of error which is unavoidable.

No constant relation between the volume indices and the cell diameters was found, and it was concluded that the measurement of cell diameters is no criterion of the richness or poorness of the red cell in protoplasm.

TABLE IV.

Diurnal Variations in Normal Individuals.

Individual and Date.	Time of Day.	Haematocrit Reading.	Haemoglobin %.	R. B. C. per c.mm.
G. G.	26.1.21	10.45 a.m.	50	5,368,000
		11.15 a.m.	50	5,488,000
		12.45 p.m.	50	—
G. H. R.	3.1.22	8.30 a.m.	53	5,464,000
	9.0 breakfast	9.30 a.m.	54	4,944,000
	1.0 lunch	2.0 p.m.	50	5,296,000
		19.1.22	51	5,072,000
		22.1.22	51	5,456,000
		22.1.22	54	5,400,000
5.30 tea	26.3.22	5.0 p.m.	48.2	—
		6.0 p.m.	50	—

TABLE V.

Diurnal Variations in Disease.

Individual and Date.	Time of Day.	Haematocrit Reading.	Haemoglobin %.	R. B. C. per c.mm.
Diabetes	30.1.22	10.45 a.m.	44	4,520,000
		2.30 p.m.	39	4,224,000
	6.2.22	10.30 a.m.	41	4,592,000
Chronic empyema	27.1.22	10.30 a.m.	32	4,400,000
		2.0 p.m.	34	4,592,000

Diurnal variations. Hedin (2) found a dilution of the blood after meals; a 12.6 per cent. variation was the greatest that he found with his own blood. Lloyd Jones (23) found that the specific gravity of the blood was reduced by food.

Dreyer, Bazett, and Pierce (24) found variations of a similar nature working with haemoglobin as the indicator. The widest variation which these workers published was a 10 per cent. variation.

In this work, using the haematocrit, an 8 per cent. variation was the greatest encountered in normal blood, as recorded in Table IV.

In diabetes, Epstein (15) found a variation of 14.8 per cent. after two hours. In this work a 10 per cent. variation was found in a case of diabetes as recorded in Table V.

Conclusions.

1. The haematocrit is an accurate instrument under the following conditions: where the capillary tubes have a bore of 0.5 mm.; where whole blood is used and where a haematocrit 'head' with an adjustable screw is in use which will prevent blood escaping from the capillary tubes. The centrifuge must be capable of a speed of at least 4,500 revolutions per minute, at which speed the red cells of normal blood are completely sedimented in from 5 to 10 minutes; the higher the speed the more rapidly is sedimentation completed.

2. The addition to the blood of citrate or oxalate vitiates the haematocrit readings by reducing the corpuscular volume per cent., unless a particular proportion of citrate to blood be chanced upon which happens to be isotonic to the particular blood under examination. The haematocrit value is reduced generally by 14 per cent. when salts are used, as compared with the values obtained by whole blood determinations. Whole blood haematocrit values were found to be more accurate than citrate values.

3. A rapid sedimenting rate of the red blood cells was observed in a number of cases in which death was imminent in five; three were cases of acute bacterial infection, and two were cases of nephritis. The rapidity of sedimentation is not in direct ratio with the poorness of the blood in corpuscular volume nor in haemoglobin content.

4. A low volume index is a rare phenomenon. It is sometimes fictitiously presented when too high a cell count has been made. The cell count appears to be higher than it actually is in blood whose sedimenting rate is rapid. A low volume index may be encountered where the haematocrit reading is lower than it actually should be on account of the escape of some of the column of the red cells from the capillary tube.

A high volume index is found in pernicious anaemia and fictitiously where the haematocrit reading is higher than it should be on account of insufficient sedimentation of the red cells.

5. The measurement of cell diameters is no guide to the richness or poorness of the red cell in protoplasm.

6. The advantages of the use of the Volume-Colour Index over that of the colour index are only present in those cases where the red cell count is

misleading as a guide to the true volume of the corpuscles; that is, where the cells are smaller than usual or poorer in protoplasm, and where they are larger than usual or richer in protoplasm than normal cells.

Wherever the cell count is inaccurate, as it tends to be in rapidly sedimenting bloods, the Volume-Colour Index is a truer index of the red cell capacity for haemoglobin than is the colour index.

7. The Volume-Colour Index lies within normal limits, 0.90-1.00, in nearly every diseased state, with the exception of chlorosis, cancerous anaemia, the terminal stages of pernicious anaemia, and haemorrhage during the six weeks subsequent to the loss of blood.

8. In septic anaemia a normal Volume-Colour Index is found, and this serves to differentiate it from a cancerous anaemia.

In concluding this paper, I wish to express my thanks to Professor Francis R. Fraser, Director of the Medical Unit of St. Bartholomew's Hospital, for suggesting this work to me, and for his many kindnesses and valued advice in connexion with it; and to Dr. George Graham for so kindly correcting the proofs and for his generous help.

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ENDOCARDITIS LENTA

By H. J. STARLING

With Plates 6 and 7

Introduction.

THE occurrence of a chronic or subacute form of infective endocarditis was first brought to the notice of the medical profession by Sir William Osler at the meeting of the Association of Physicians in 1908, when he reported 10 such cases. In the following year Sir Thomas Horder, again at a meeting of that association, gave an analysis of 150 cases of infective endocarditis, from which he separated 88 as being of a subacute and 18 of a chronic type.

Libman, in 1910 (1) and subsequently, reported at length on a great number of these cases, which he termed subacute infective endocarditis. This writer claimed that there were two stages in this disease: an early stage in which the specific organism—*Streptococcus viridans*—could always be discovered, and a later bacteria-free stage.

In August 1918 I described the first five cases of a great number which were subsequently admitted into the Military Heart Hospital, Colchester (2); Lewis makes a special reference to this disease in his book *The Soldier's Heart and Effort Syndrome* (3); the peculiar characteristics of the disease were set forth in an exhaustive analysis of 55 cases by Thomas Cotton (4).

I have, however, been much impressed by overwhelming evidence that cases of this disease still escape recognition and diagnosis in very many instances. I believe that its insidious onset and long duration are not fully recognized, and therefore desire again to call attention to this most interesting type of infective endocarditis, with especial reference to the cases which have been under my care at the Norfolk and Norwich Hospital since April 1919.

Sir Thomas Horder, in his well-known paper on this subject (5), divided infective endocarditis into five varieties: (i) latent; (ii) fulminating; (iii) acute; (iv) subacute; (v) chronic.

It is the last group which I propose to discuss in this paper.

Some cardiologists would also add a sixth variety, namely, rheumatic endocarditis, for the reason that this type progresses downhill, and ends fatally, by means of re-infection. This is undoubtedly the case, but I hope to show that the variety under discussion differs as markedly from rheumatic endocarditis as it does from the acute infective variety.

Symptoms.

There is practical unanimity as to the characteristic symptoms of this disease; the figures of their incidence here recorded are compiled from two groups of cases.

Group A. Thirty soldiers under treatment at the Colchester Heart Hospital, 1917-19.

Group B. Twenty-two discharged soldiers who were admitted into the Norfolk and Norwich Hospital between June 1919 and April 1922.

Pallor. Group A, 95 per cent.; Group B, 90 per cent. In the second group of cases, although there is evidence to conclude that the infection was contracted while on active service, yet the date at which they began to break down was subsequent to the armistice, in some cases a year or two afterwards. Some of the cases were admitted into hospital in whom the complexion was of a healthy red, in others a slight pallor could only be detected in the skin of the temples and forehead or underlying the flush of the cheeks. But as the cases progress the pallor becomes more noticeable.

In nearly every case, however, a lemon-yellow pallor can be observed in the skin of the body and limbs where it is protected from the light, and the degree of pallor is always more advanced in these regions than it is on the face. This contrast is an important help in diagnosis, especially in those cases which at first possess a healthy florid complexion. A few cases showed no facial pallor up to the date of death.

The late incidence of pallor also differentiates the chronic infective type very strikingly from cases of acute and subacute infective endocarditis.

Anaemia and leucocytosis. In Group A the following figures were obtained in blood-counts from ten patients:

Average: Red blood-counts	4,380,000	White cells,	11,670	Haemoglobin	55 %
Highest: " " "	5,500,000	" "	16,500	" "	70 %
Lowest: " " "	3,200,000	" "	7,500	" "	44 %

In Group B. Ten cases:

Average: Red blood-counts	4,631,000	" "	8,560	" "	54 %
Highest: " " "	8,100,000	" "	12,400	" "	64 %
Lowest: " " "	3,000,000	" "	1,300	" "	40 %

The usual features, therefore, are a small diminution of red cells, a reduction of haemoglobin by 50 per cent., and a diminution of white cells, amounting to a marked leucopenia in some cases. The second group of figures is probably the most reliable, owing to the fact that they were taken from pensioners in a more normal condition of life than the first group, all of whom came direct from overseas.

Clubbing of fingers. This is a most important clinical sign. It is evidence not only of the infective character of the disease, but also of the length of its duration. It is not seen in the fulminating or acute varieties, and I have not noted its presence in any one of some hundreds of cases of simple rheumatic endocarditis of all grades. I have seen clubbed fingers well marked in a case

eleven months before death. I have seen it in a comparatively early stage, gradually increasing as the case progressed, the thumbs being first affected, the forefingers next, and then the rest of the fingers. It frequently involves the toes, the big toes being primarily affected, but only after the fingers have shown the characteristic change.

There is every reason to believe that the valvular lesions precede clubbing by a very considerable period of time, as is shown by the following case:

Case I. A. D., aged 37. An agricultural labourer. Scarlet-fever at 21 years; no other illnesses. A family history of tuberculosis. Enlisted 20.1.15, R.F.A. To France, September 1915; to Italy, November 1917. Returned to France, March 1918. Demobilized June 1919. Had influenza in France, March 1918, but no wounds or other illnesses.

He stated that he was short of breath on exertion soon after enlistment, but this passed off, and he did his full military duty throughout the war. After his demobilization he returned to his pre-war employment, but six months later he began to be short of breath, and in February 1920 he saw a doctor who expressed his surprise that he had been discharged in an A 1 category. He was laid up for a few weeks, but returned to work until January 1922, when he again became unfit.

He was admitted to hospital in February 1922, a finely-built man, with full red complexion but some pallor of the skin of the body. The heart was not enlarged, but a long diastolic blow could be heard over the upper end of the sternum. He had some pyrexia for ten days, but after that his temperature was normal for the rest of his seventeen weeks in hospital.

He was sent home at his own request on May 2, 1922. On his discharge, his general condition was improved, there was no clubbing of the fingers, nor was the spleen palpable. He attended weekly at the heart clinic, and three weeks later early clubbing of the fingers and a palpable spleen, with some increase in pallor, were noted for the first time.

On June 5, 1922, while out walking, he was taken with right hemiplegia and aphasia, and had to be carried home to bed. He recovered from his aphasia and regained the use of his leg, but died on September 14, 1922. Had the hemiplegia occurred a month earlier it would have antedated the occurrence of clubbing of the fingers and enlargement of the spleen.

Endocarditis. All the cases have had well-marked valvular lesions at the time the diagnosis was first made. The aortic valves are chiefly affected, either alone or in conjunction with the mitral valves. Signs of mitral stenosis alone were observed in only one case of each of the above groups. Cotton records mitral stenosis alone in four out of his fifty-five cases (4).

Enlargement of the heart. This is seen in every case towards the end of the illness, but is frequently absent in those cases which come under observation at an earlier period. To this comparative immunity of the heart-muscle from infection must be ascribed the extraordinary capacity for effort and strain which is so often recorded up to quite a late period of the illness. Orthopnoea is conspicuous by its absence, the patients lying comfortably flat in bed, with only one pillow, until quite a late period.

Enlargement of the spleen. Group A, 81 per cent.; Group B, 100 per cent. This is an important diagnostic symptom, as evidence of probable infarction. The primary infarction is probably an early occurrence, and I believe that

infarction may take place before the spleen is sufficiently large to be palpable. On the other hand, the spleen very occasionally becomes fixed by adhesions under the costal arch, and may never be palpable unless its enlargement is considerable. A palpable spleen has been observed eleven months before death. Infarction of the spleen often gives rise to intense abdominal pain, and a friction rub is sometimes to be heard over the organ. In other cases no history of pain or discomfort is obtainable even after the spleen is considerably enlarged.

Gross embolism. Group A, 39 per cent.; Group B, 68 per cent. Arterial embolism has been observed in every region of the body. In the second group of twenty-two cases there were:

(1) Right hemiplegia with aphasia, seven cases. Five of these completely recovered to die later of heart or renal failure. One died as the direct result of a massive cerebral haemorrhage which took place while the patient was rowing on the river. The last died of a cerebral haemorrhage following the previous cerebral embolism.

(2) *Two* cases in the posterior tibial artery. One of these cases was admitted to hospital, not for any affection of the heart, but for a huge aneurysm in the calf.

(3) *One* case of embolism in a branch of the superior mesenteric artery, death occurring within ten hours.

(4) The other arteries involved were: facial 2, gastric 1, brachial 1, optic 1, and several small subcutaneous branches.

When the artery involved lies subcutaneously, there occurs a considerable area of inflammation involving the skin and sometimes leading to definite lymphangitis farther up the limb. The pain, redness, and swelling clear up in three to five days.

Suppuration has never been observed in any of these infarcts.

It is of interest to note that even though an embolus may result in hemiplegia and aphasia, yet the patient does not always lose consciousness. In Case I the patient was out walking in the country and was seen to stagger by a woman who observed him from a discreet distance, thinking he was drunk. When he failed to return home, his family went to look for him and found him lying at the bottom of a dry ditch. The green sides of the ditch were torn up and crushed by his endeavours to pull himself out. When he recovered from his aphasia, the patient stated that at the onset of the attack he felt he had no control of his limbs, and he staggered and ran without volition until he fell in the ditch. He did not lose consciousness, and only desisted from his efforts to get out from sheer fatigue at their ineffectiveness.

Another patient still under my care, who had a left hemiplegia, and whose arm and lower part of the face on the left side are still paralysed, also did not lose consciousness. He was at his work as an hotel cook, when he suddenly felt a tingling in his fingers; this spread up the left arm to the left side of the chest and affected his heart, which he felt as 'if it were being torn out of the chest'. The tingling then went down the left leg to his toes, and he had a violent pain in the left side of his head. He then called for assistance and was removed to an infirmary.

In two cases a fatal cerebral haemorrhage occurred on the same side as, and after, a previous cerebral embolus.

Petechiae. Group A, 58 per cent.; Group B, 64 per cent. The incidence of petechiae in these cases would be higher if the patients were examined carefully every day. They are seen most frequently in the mucous membrane of the lips or conjunctivae, in the axillae, in the supra-clavicular fossae, as well as in other parts of the body. They come out in successive crops and last from three to five days. In the majority of cases they have occurred singly and have not formed a marked symptom of the disease.

Osler's nodes. At one time these lesions were thought to be pathognomonic of subacute infective endocarditis (6). In my original paper I mentioned them as occurring in two out of the five cases described. In these cases they occurred six months and four months respectively, previous to the patients giving up full duty overseas. I have only obtained a history of their occurrence in four cases subsequently, and in these they appeared to be an early manifestation which did not recur at a late period.

Sweating. This is a common symptom, usually occurring at night-time and not necessarily associated with pyrexia. I have in many cases obtained a history of its presence some months before the patient became seriously incapacitated.

Rigors are conspicuously absent.

Pyrexia. In the majority of these cases the absence of any fever is remarkable. In Case I, after ten days of pyrexia following admission, the temperature remained below 99° for a period of seventeen weeks until his discharge. In most cases there are periods of two to three weeks in which no fever occurs. In some cases the temperature ranges from 99.4° to 99.6°. In a few cases there may be some weeks of a temperature ranging between 99° and 101°. In all cases, at some time or another, there are occasional periods of marked pyrexia, the temperature rising to 101° or higher within eight to twelve hours, and then subsiding to normal within three to seven days. These periods of marked pyrexia, and probably those of a minor degree as well, are the result of embolic processes in the spleen, the kidneys, and other areas of the body. Apart from this the illness is apyrexial. My colleague, Dr. Edgar Todd, while house-physician at the Norfolk and Norwich Hospital, compiled the following table of incidence of fever in a group of six cases:

Details of temperature, &c., in six cases:			
Total duration of time spent in hospital	.	.	354 days
Temperature normal or subnormal on	.	.	180 "
" between 98.6° F. and 99° F. on	.	.	69 "
" " 99.2° " 100° "	.	.	59 "
" " 100.2° " 101° "	.	.	32 "
" above 101° F. on	.	.	14 "
Total duration of pyrexia	.	.	174 "
Marked embolic phenomena observed on	.	.	87 "
Pyrexia occurred apart from above on	.	.	87 "

Urine. In about 50 per cent. of the second group of cases albuminuria was not noted until about one month before death. Its presence depends primarily on multiple infarction of the kidneys, generally microscopic, sometimes macroscopic. It also depends on the amount of venous congestion present, due to cardiac failure.

The presence of blood in the urine was noted in 60 per cent. of twenty cases. But it can be found more frequently if the urine is subjected to microscopical examination after centrifugalization. The presence of blood is of importance as an aid to diagnosis.

Only five cases showed features of general nephritis, and in these the essential symptoms were manifested two to three months before death.

The following cases are given as typical of this type of infective endocarditis:

Case II. R. F., aged 37. Farm labourer, no illnesses pre-war nor during service. Enlisted October 1915, trained without difficulty. To France October 1916; G.S.W. of thigh March 1917; eleven months in hospital. On discharge from hospital, April 1918, he was short of breath, and this had been getting worse since. He was sent to see me, November 12, 1919, and was admitted at once into hospital.

On admission, a man of fine physique, much pallor of face and body, fingers showed advanced clubbing, spleen much enlarged and tender, scattered petechiae on chest and abdomen. The heart was much enlarged, a long presystolic rumble and systolic blow at the apex, a long diastolic blow at the base. His progress downhill was very slow. He only required one pillow on which to sleep until April 1920, when oedema of the legs and back and ascites gradually increased. During the whole of this period his temperature remained below 99°, except for intervals of three to five days, when it rose to 100°. He died on May 4, 1920.

Autopsy. The aortic valves were completely replaced by a calcareous reticulum, calcareous nodules filling the sinuses of Valsalva. There was a large calcareous vegetation on the mitral valve, which was crumpled and covered with sessile calcareous deposit, which also was present on the chordae tendineae, which were much thickened, many broken. Spleen much enlarged, dotted with many infarcts, none recent.

Case III. F. N., aged 24. A gardener pre-war, had never been on his sick club. Enlisted December 1914, infantry, no difficulty with the training. In 1915 slight G.S.W., then had 'debility', and was off duty for three months. After return to duty he had bronchitis, and after this was placed in Class B. He was then transferred to the Machine Gun Corps, and returned to France March 1918, feeling all right. He was on full duty and went as far as Mons in the 'big push'. He remained in France, but in August 1920 he had severe gastritis for three weeks and had not felt well since, although he remained on full duty.

In February 1921 he had a board while in the army, and V.D.H. was diagnosed, and he was forthwith discharged. He was seen by a medical board in April 1921, and was found to have a fully-developed aortic regurgitation with mitral stenosis. The heart was not enlarged. The spleen was palpable, the fingers showed definite clubbing. His colour was good although the skin under his clothes was a dead white. He was able to walk three to four miles at a brisk pace, but was short of breath going uphill. He was admitted into hospital for three months and then discharged to his home. Early in December 1921, he had

aphasia and right hemiplegia, both of which cleared up completely. He died on March 4, 1922, eleven months after he was first seen by the Medical Board, with fully-developed symptoms of this disease.

Aetiology.

It may be urged that the incidence of this disease, as it occurs amongst discharged soldiers, is an exaggerated one, due perhaps to better facilities for hospital treatment provided by the Ministry of Pensions. For the purpose of comparison, therefore, I analysed the post-mortem records of the Norfolk and Norwich Hospital for two periods, each of four years (April 1910–April 1914 and April 1918–April 1922), excluding the years 1914–18 as being liable to error owing to stress of work during this period.

Relative Incidence of Infective Endocarditis as shown by the Record of Autopsies at the Norfolk and Norwich Hospital in the Years 1911–14 and 1918–21.

1911.	No. of autopsies	. . .	93	Infective endocarditis	2 = 1 in 46	
1912.	"	"	99	"	3 = 1 in 33	
1913.	"	"	95	"	3 = 1 in 32	
1914.	"	"	81	"	2 = 1 in 40	
1918.	"	"	(no pensioners)	47	"	1 = 1 in 47
1919.	"	"	(civilians)	66	"	0 = 0 in 66
	"	"	(pensioners)	11	"	3 = 1 in 4
1920.	"	"	(civilians)	83	"	5 = 1 in 15
	"	"	(pensioners)	14	"	6 = 1 in 2.3
1921.	"	"	(civilians)	91	"	3 = 1 in 30
	"	"	(pensioners)	14	"	6 = 1 in 2.3

N.B.—Nine out of the fifteen affected pensioners were primarily admitted as civilians.

All types of infective endocarditis are included in the civilian figures, which show a ratio to all autopsies of 1 in 32 to 1 in 46 in the period preceding the war, and of 1 in 15 to 1 in 47 in the period after the war. But in this latter period the incidence amongst discharged soldiers is very marked. The ratio compared with civilians is 3 to 0 in 1919, 6 to 5 in 1920, and 6 to 3 in 1921.

The civilian incidence is much the same post-war as it was pre-war, except that in 1920 it was 1 in 15, which, however, counterbalances the preceding year, in which it was 0 to 66.

There were admitted into the Norfolk and Norwich Hospital, between June 1919 and April 1922, ten civilians and twenty-six discharged soldiers suffering from infective endocarditis.

Of the twenty-six discharged soldiers, nine were admitted to hospital primarily as civilians (but not so included in the above figures), the majority being subsequently transferred to the Pensioners' Ward.

Of the ten civilians, eight were examined *post mortem*, and these will be discussed with the other autopsies. The two remaining may be briefly indicated:

Case I. Male, aged 29. Rejected for army service on three occasions between 1915–17 for heart trouble. Had influenza sixteen months before

admission to hospital in 1920 and died in a few days. No mention of clubbed fingers or enlarged spleen. No P.M.

Case II. Female, aged 40. Had anaemia in November 1920, oedema of legs in December 1920, admitted to hospital April 1921. Cystic mole removed from uterus. Intense pallor, systolic murmur over praecordium, pyrexia up to 102; death in four weeks. No clubbing of fingers, spleen not palpable. No P.M.

Ages of Cases of Infective Endocarditis admitted to Hospital between June 1919 and April 1922.

		Age.	1-10.	10-20.	20-30.	30-40.	40 and over.
Civilians	Female.	Total 4	—	—	1	1	2
	Male.	Total 6	2	1	2	—	1
Soldiers		Total 26	—	—	14	7	3
	Age not recorded in 2 cases						

But much more remarkable than the actual incidence among discharged soldiers and civilians is the difference between the types of disease in these two classes. The records of the illness of the civilian cases, in all except four, show one or more of the following features:

- (1) Sudden onset with rigors and severe pyrexia, or severe pyrexia throughout the illness, which was of short duration.
- (2) Definite infection of joints, lungs, or other organs to which the endocarditis was secondary.
- (3) The presence of a primary disease such as carcinoma.
- (4) A long history of cardio-vascular disorder, or repeated and recent attacks of rheumatic fever.

It is quite clear, therefore, that these cases belong to Sir Thomas Horder's groups 1, 2, or 3, and not to the last two groups.

In no one of these cases was there any post-mortem evidence of the healing process which is so characteristic of the subacute variety. The vegetations were described as sessile, red, or fungating, and in some cases the infarcted areas showed signs of breaking down, which, in my opinion, never takes place in the chronic variety of this disease.

The four exceptions comprised:

- (a) A case in 1912, of which I can find no notes.
- (b) A case in 1920, following influenza.
- (c) A case in 1921, also following influenza.
- (d) A case in 1921, complicated by the presence of enteric fever.

The last three cases certainly belonged to the subacute variety, but were characterized by intense pallor, considerable pyrexia, and profuse sweating, the illness being severe from the onset of the symptoms. Judged on the same evidence as that obtained in the cases of discharged soldiers, case (b) had a duration of four months, case (c) of nine months, and case (d) of twelve months.

In the eighteen civilian autopsies the valves were affected as follows:

mitral, 6; mitral with tricuspid, 2; mitral with aortic, 2; aortic, 5; tricuspid, 1; pulmonary, 1; no mention, 1.

From the group of twenty-six soldiers referred to above, four cases are excluded as not belonging to the special type under discussion.

These four exceptions are:

(1) A case of acute infective endocarditis following pneumonia.

(2) and (3) Cases of subacute infective endocarditis, in which the history, progress, and post-mortem appearances resembled the civilian cases of this type just referred to. These two cases had histories of both old and recent rheumatic fever with endocarditis.

(4) A case who served in France from 1916 for three years, in Ireland in 1919, and died two days after admission. No P.M. allowed. Notes very scanty.

This leaves the group of twenty-two cases, already referred to as Group B, for comparison with Group A.

Service in France.

Group A. All cases served in France, except one who served in Italy.

Group B. All cases served in France.

Date of Service Abroad.

Group A. 30 cases: 27 were serving in France in 1916;
1 commenced serving in France in 1917;
in 2 no record of service is available.

Group B. 22 cases: 17 were serving in France in 1916;
4 commenced serving in France in 1917;
1 " " " 1918.

Illnesses previous to Enlistment.

	Group A.	Group B.
Chorea	0	1 in childhood
Rheumatic fever	3 in childhood	0

Illnesses during Army Service.

	Group A.	Group B.
Rheumatic fever	7	—
Rheumatism	1	4
Influenza	7	3
Trench fever	—	2
Bronchitis	—	2
P.U.O.	1	1
Scarlet fever	—	1
Dysentery and malaria	2	1
Wounds	6	9
Septic infection (impetigo, boils, &c.)	1	5
Prisoner of war	0	2

No Illnesses either before or during Army Service (excluding wounds).

Group A.	Group B.
11	8

	Wassermann Test.	Group A.	Group B.
Positive		1	4
Negative		10	16

Average Period of Service.

Group A.	Group B.
3.5 years	3.3 years

It will be seen from the above figures that the incidence of rheumatic fever, both before and during army service, is higher in the Colchester Group A than in the Norwich Group B. For many reasons it was impossible in the former group to draw a definite line between the subacute and the chronic cases. All the cases had been subjected to severe physical stress, the result of front-line service, for unknown periods after the disease was fully developed, and the cases were therefore admitted to the Colchester Hospital in a much more advanced stage than in the majority of the cases of Group B.

Further, at that time attention was chiefly directed to the differentiation of the subacute from the acute type of infective endocarditis. From the perusal of the case sheets, the temperature charts, and the duration of the illnesses, it may be stated, however, that quite 50 per cent. of these cases belonged to the chronic rather than the subacute variety. The figures referring to the absence of illnesses, either before or during army service, are about the same in each group, namely 33 per cent.

Further details of Group B are as follows:

	<i>Physique.</i>
Finest possible	13
Good	5
Spare but muscular	4

Incidence of Pensions.

When first seen with the disease fully developed—

- 11 were drawing no pension.
- 3 were drawing a pension for G.S.W.
- 1 was drawing a pension for shell shock.
- 1 was drawing a pension for D.A.H.

In this type of infective endocarditis, which seems to be best described by the term 'endocarditis lenta', the following points are significant:

(1) The absence of any predisposing or specific cause of infection, as contrasted with the civilian cases noted in the P.M. records of the Norfolk and Norwich Hospital.

(2) The very low incidence of rheumatic fever as contrasted with the following figures given by various writers on this disease in the years preceding the war:

	Cases.	History of Rheumatic Fever.	Mitral Lesion.
Osler (7)	10	6	8
Horder (8)	18	'in most cases'	—
Schottmüller (9)	5	4	3 (out of 4 autopsies)
Libman and Celler (10)	19	'nearly always'	{ 10 mitral 3 aortic 7 mitral and aortic

Dr. Carey Coombs has kindly given me some figures from cases of the sub-acute and chronic types seen by him in his own (civil) practice since 1919.

Total No. of Cases.	History of Rheumatic Fever.	Mitral Lesion.
30	12	5
Of whom were ex-soldiers with overseas service) 20	4	0

(3) In the above figures the mitral valve is chiefly and primarily affected in the civil cases occurring both before and after the war. In only one out of Group B, twenty-two cases, was the mitral valve solely affected; in all the rest the aortic valve was primarily if not solely affected.

(4) In only one of thirteen autopsies from Group B was there any evidence of scarring of a valve from previous rheumatic infection. A similar picture is given by Sir J. Rose Bradford, in the Lumleian Lectures for 1920, on his experiences with the British Expeditionary Force (11).

His conclusions may be summed up as follows:

(1) Infective endocarditis was uncommon in the wounded, notwithstanding the prevalence of septic infection.

(2) A considerable number of acute and rapidly fatal cases of infective endocarditis occurred, in which no primary source of infection could be discovered *post mortem*.

(3) These cases were not cases of old valvular disease, but the acute infection had apparently attacked healthy valves, and there was no recent antecedent illness, e.g. pneumonia, to explain the condition.

The disease was apparently primary in the endocardium.

Bacteriology.

In only four out of sixteen cases was a positive blood culture obtained. In each case a streptococcus was grown, occurring in pairs or short chains. In no case was a subculture obtainable. This negative result is in marked contrast to those cases recorded by Libman (1), in which a positive culture of *Streptococcus viridans* was obtained in every case at some time or another. Sir Thomas Horder (5), in reference to all types of infective endocarditis, states that 'when every facility is given to the micro-organism to grow in the media used, it may be said that positive cultures are obtained sooner or later in 90 per cent. of the cases'. In writing to me recently, however, he stated that he had experienced much the same negative results as myself and many other workers.

Post-mortem Lesions.

The low virulence of the bacterial agent, when found, forms the key-note of the lesions it creates. Despite the frequent emboli in various organs and parts of the body, in no single case was there seen an infarction breaking down. The

reverse is the case in infarctions occurring in the acute and subacute varieties of this disease.

The spleen is invariably enlarged, and usually shows multiple infarcts, both recent and old. In only one out of thirteen autopsies was no infarct present in the spleen, which, however, was much enlarged.

Valvular Lesions.

In rheumatic endocarditis the recent vegetations have a sessile, warty, or translucent appearance. In healed lesions the scar tissue is firm, white, and glistening.

In acute and subacute infective endocarditis the vegetations have a fungoid consistency and appearance; they are soft to the touch, and, if calcareous change has occurred, they are friable. If ulceration or perforation of a valve has taken place, the edges are ragged and there is little or no sign of fibrous change.

In these varieties the mitral valve is chiefly and primarily affected in the majority of cases, the aortic valve being involved secondarily.

The valvular changes in endocarditis lenta are quite characteristic, and the type of the disease can be diagnosed with considerable exactitude from their appearance. Fibrosis and firm calcareous change are most marked, and the aortic valves are chiefly involved.

In thirteen autopsies the aortic valves were solely affected in six; in the rest both aortic and mitral valves were involved, but there was clear evidence that the infection had begun in the aortic valve, extended to the aortic surface of the mitral valve, and thence on to the mitral valve proper.

In four of these autopsies the cusps of the aortic valves were fused together with complete absorption of the intervening septum. The edges of the cusps were greatly thickened and everted into the sinuses of Valsalva. This seems to be a peculiar feature of this disease and resembles a congenital malformation. I have, however, seen every stage of this fibrous change in other cases, from simple thickening of each cusp up to the stage of complete fusion.

With the fibrous change occurs calcification, either in the form of enormous solid masses which appear to replace the whole of one or more cusps, or in smaller masses which form a reticulum replacing the normal structure of the cusp.

In both these changes of fibrosis and calcification, although the normal tissues are lost, yet there is no appearance of ulceration, the parts are finely fibrous or calcareous, and the replacement gives the suggestion of absorption rather than of ulceration.

The appearances of the mitral valve are of a similar nature, but fibrosis is more pronounced than calcification, and, if the latter takes place, the vegetations are not so large as on the aortic valves. The fibrous change affects the valve itself, and also extends down the chordae tendineae, sometimes in the form of nodules which are firm, occasionally calcareous, but chiefly resulting in great thickening of these structures.

The thickening of the edge of the mitral valve is occasionally so pronounced that the chordae tendineae appear to be attached behind the free margin, which overhangs as a distinct ledge. As the fibrous change increases, or contraction takes place as a consequence, many of the chordae tendineae break, but this does not appear to be due to actual ulceration.

It is this thickening of the mitral and aortic valves that has given rise to the assumption that there has been previous rheumatic infection of the endocardium. The appearances, however, are quite different. The fibrous thickening is never a white and glistening scar tissue, rather it is of an indolent appearance more resembling a keloid condition. The combination of old fibrous and calcareous change, together with pedunculated and sessile vegetations, fibrous and firm, suggests very strongly that the lesions are not the result of one continuous process of infection without remission, but rather that the duration of the disease is considerable and entails infection, reaction, and healing often repeated.

In a few cases, notably that of No. 567 (reproduced in Plate VII, Fig. VI), in which, however, no evidence of reinfection was discoverable by clinical signs, the autopsy revealed not only long-standing calcareous and fibroid change, but also recent infection. At two areas, where the cusps of the aortic valves were attached to the wall of the aorta, and again on the aorta itself a little higher up, were seen discrete sessile fresh vegetations. These were about the size of a split pea and were only just raised above the normal level of the endocardium. They were semi-opaque and of a brownish hue. Dr. Claridge, Pathologist to the Norfolk and Norwich Hospital, examined sections of the vegetation from the wall of the aorta and reports as follows:

‘There is a thickening of the intima of the aorta over an area 12 mm. in length, to a depth of 1 mm. at its central part. This thickening is seen to be due to a collection of chronic inflammatory tissue under the endothelium, consisting mainly of fibroblasts with a small number of small round cells. In some parts mature fibrous tissue has formed, and here the tissue is devoid of the round cells, which are most numerous in the deeper parts, i.e. near the media. Small collections of these round cells may be seen in the media particularly associated with the vasa vasorum. The adventitia does not appear to have taken part in the changes, while in no part are there any micro-organisms to be found.’

In some of the autopsies there were seen patches of vegetations on the wall of the left auricle, in others on the aortic surface of the mitral valve or on the wall of the aorta. These patches appeared to the naked eye as a roughening of the surface of the endocardium, hardly raised above the normal level. The vegetations are finely calcareous, and in one case healing had taken place and the site was marked by fine puckering of the endothelial surface (shown in Plate VII, Fig. IV).

Duration of Illness.

From the following figures those cases were excluded who died on the day of admission or were admitted practically *in extremis* and died within one week. The onset of the disease has been reckoned from the earliest date on which dyspnoea or weakness was first noted. This estimation is justified by the fact that all had been A 1 men and had had no recent cause of infection.

Average period from onset to admission to hospital	15 months
Average period from admission to hospital to death	3.7 months
	<hr/> 18.7 months

The longest period from admission to hospital to death was eleven months. The above average represents a minimum. Stress must be laid on the fact that in many cases there has been no noticeable dyspnoea or diminished capacity for work at a date when the discovery of the fully-developed disease was accidental, due in some cases to a massive embolus. Taking into consideration the very slow progress of the disease, even when it has been first diagnosed with all the cardinal symptoms, a further period of six or probably twelve months should be added to the above figure, making a total duration of two to three years, perhaps longer.

This is shown by the following case :

Pensioner J. L. K., aged 30. A clerk. No illnesses prior to or subsequent to army service. (N.B.—This case is not included in the preceding figures.) Enlisted December 1915. To France May 1916. P.U.O. November 1916. Influenza December 1916. April 1917: G.S.W. right hand, severe sepsis. May 1917: amputation right arm, lower third, healed by first intention. December 1917: discharged from army; resumed clerical work, writing with his left hand. May 1920: left hemiplegia. November 1920: aortic regurgitation first noted. January 1921: subacute infective endocarditis first diagnosed. February 1921: died of cerebral haemorrhage.

In this case the pensioner had had no infective illness (apart from the gunshot wound) from the date of his discharge to the date of his death. Three years elapsed from the date on which he was wounded to the occurrence of the first embolus, and then nine months from the latter date to the date of his death. Being in receipt of a pension for his wound, his heart did not require to be examined until November 1920, when the cardio-vascular symptoms were so marked as to be noticeable. He had trained himself to write with his left hand after his discharge and was employed as a clerk. Even in January 1921, when I first saw him, he made no complaint of any dyspnoea. He presented the appearance of robust health with a ruddy complexion. Nevertheless, he had a gross aortic insufficiency with enlarged spleen and marked clubbing of the fingers.

This is only one example of many cases who showed no disability until just before death.

Other cases may be briefly quoted, bearing in mind that each case was fully developed when first seen.

(1) A. F., aged 27. Worked as a gardener until he consulted a doctor for the first time in September 1921, who ordered his immediate removal to hospital on a stretcher.

(2) A. H., aged 43. Carried on heavy work until one week before admission to hospital, where he died one month later.

(3) A. B., aged 27. Eight months before admission was passed as a first-class life for a life insurance (the examination seems to have been somewhat casual). Six weeks before admission was running in 100 yds. race and wrestling with his brother. Up to one week before admission he was canal-digging. Admitted to hospital and died the same day from an embolus of the superior mesenteric artery.

(4) W. H., aged 22. A printer's mechanic. Was on a holiday at Yarmouth and was sent to hospital for a cerebral embolus. Died six months later.

(5) W. R., aged 30. A clerk, in good health and full work. While rowing on the river had a massive cerebral haemorrhage from which he died the same night (Plate VI, Fig. III).

(6) R. H., aged 30. Heavy agricultural work till January 1920; four weeks later admitted to hospital straight from first medical board and died in August 1920.

Mode of Death.

Of the twenty-two cases in Group B, thirteen died of heart failure, complicated in some cases by renal symptoms; five died of renal symptoms; three died as the result of arterial embolism; one died after operation for intestinal obstruction (the second laparotomy in three months).

Recovery.

No case in which I have been able to diagnose this disease without any doubt has ever recovered. There are, however, a considerable number of cases which are still under observation and which I suspect are healed cases of this particular type. I give brief notes of one of them:

B. C., aged 29. Farm labourer. No previous illnesses. Enlisted 1914; France and Italy three years; carried on full duties at the Front till February 1919. Had influenza 1915 and 1916. Was in hospital for four months for G.S.W. right arm. Thought his present condition began then. First seen in January 1920. A big powerful man, pink flush on cheeks, background slight pallor, skin of body almost a lemon yellow. Had sweated at night for preceding two months. Heart A.B. sixth space, internal to nipple line. Impulse heaving. A blowing systolic apical bruit in all postures and phases of respiration. Fingers not clubbed, spleen not felt, but deep palpation over it is painful. Admitted to hospital for six weeks, slight occasional pyrexia (to 100). No albumin or blood in the urine. Blood culture negative. Red b.c. 3,625,000; white cells 7,100. Hb. 32 per cent. Wassermann negative. His only complaint was that of exhaustion during hard work. He was discharged to work.

He was last seen in January 1922. Colour very good, skin of body pale.

Spleen tip palpable and very tender. No clubbing of fingers. The apex beat was in same position, the bruit was less harsh but still present. He was doing a full day's agricultural work.

At the annual meeting of the British Medical Association at Cambridge in 1920, as a contribution to the discussion on subacute infective endocarditis, I referred to two cases of this disease in which healing had taken place:

Case I, mentioned by Dr. Glynn in the Lumleian Lectures for 1903, in which, nineteen years after recovery from an illness thought to be this disease, death took place, and calcareous vegetations were found on the anterior surface of the mitral cusp.

Case II. Dr. Theodore Fisher, in the *Medical Chronicle* of 1903, recorded the death of a woman after miscarriage, and found at the autopsy calcareous and fibrous masses on the posterior surface of the auricle and great thickening of the edge of the mitral valve. Four years previously this woman had been a patient at the Bristol Royal Infirmary and had been diagnosed as suffering from 'malignant endocarditis'.

I have had several cases under observation for the past three years which I believe to be cases of healed 'endocarditis lenta'. In two of them the spleen cannot be felt, but palpation in this region produces pain. In none of them, however, is there present clubbed fingers, so that a definite diagnosis cannot be made unless the case comes to an autopsy. One cannot but believe that some of these cases do recover in view of the long duration of the disease and the evidence of healing that is observed in all the lesions seen at the autopsy.

Caesar Amsler (12) has recorded sixteen cases, in all of which a bacterial origin of the valvular disease was probable, and the changes due to arteriosclerosis and old age could be excluded. All these patients died of an intercurrent disease, and the condition of the heart was not discovered until an autopsy was performed. He further states that during the preceding four years chronic and relapsing verrucous endocarditis had been found seventy-six times among the necropsies held in the Basle Pathological Institute. In no fewer than sixteen, or 21 per cent., had recovery occurred so far that perfect functional results were obtained. The paper quoted does not give sufficient details to show to which type of infective endocarditis these cases belonged.

Summary.

Endocarditis lenta is a type of infective endocarditis with the following characteristics:

1. It occurs in individuals of fine health and physique who have had little or no previous illness.
2. The majority of those suffering from it have undergone a considerable degree of physical stress, e.g. those who were serving in the fighting line in the years 1916-17.

3. It is marked by an insidious onset, very slow progress, long duration, and, as far as is known, a fatal termination.

4. Rheumatic fever is not a determining cause of its occurrence, nor is there any infective agent known as its predisposing cause, except, perhaps, sepsis in the form of impetigo, boils, or wounds.

5. It may be present in a well-developed stage without the individual being in any way incapacitated for work. In such a case the patient may die from the results of a massive embolus without having been aware that he had any disease of his heart.

6. Its course may be afebrile throughout. Pyrexia, when it does occur, is usually the result of emboli.

7. Recovery is suspected to have occurred, but there are no definite proofs.

8. The infection is primary in the endocardium. The post-mortem appearances show evidences of infection, reaction, and healing, but no evidence of previous rheumatic endocarditis.

9. It represents the dividing line between rheumatic endocarditis and other forms of infective endocarditis. It resembles the former in its slow progress, formation of fibrous tissue, and evidences of healing, absence of necrotic change in the areas of infarction, and apyrexia. It differs greatly from rheumatic carditis in the frequent occurrence of emboli, in the absence of myocardial infection, in its fatal termination, and in the marked changes in the structure of the valves.

10. The infection is due to a streptococcus of very low virulence which can only infrequently be cultured from the blood, and can be found only with difficulty in sections through the affected endocardium.

11. Its presence, even in an advanced stage, is so insidious that it frequently escapes recognition.

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DESCRIPTION OF PLATES.

PLATE 6, FIG. I. Aortic valves. Considerable difficulty was experienced in opening the aorta, as all three cusps were adherent together except at one small opening by the anterior wall of the aorta. The under surface of each cusp is a solid calcareous mass. The mitral valve (not shown) was much thickened along the apposing edge, with small fibrous nodules running down the chordae tendineae, which were thickened throughout their length.

FIG. II. Aortic valves. Two cusps have been fused together, no trace being left of the intervening septum, and nearly filled with one big mass of solid calcareous material. The cusp on the right is in an earlier stage of a similar process, is partly fused with its neighbour, the intervening septum being much thickened and in process of disappearing.

FIG. III. Aortic valves. Two cusps fused together and showing much fibrous but not much calcareous change; a perforation is seen of and to the left of the combined cusps which is filled up with calcareous nodules. The cusp on the right is intact but becoming fibroid, and a small calcareous tag with other nodules is seen forming on the corpus arantii.

PLATE 7, FIG. IV. Aortic valves. All these cusps are fused together. The cusps are much distended and their edges are covered with sessile calcareous nodules.

FIG. V. Mitral valves of preceding figure. Enormous distortion due to calcareous masses on edge of valve running down the chordae tendineae, which are greatly thickened; some are fused together, others broken, so that they are practically represented by three thick ropes. On the auricular wall (high up on the right of the picture) the endothelial surface is much puckered, the result of healing of a mural vegetation.

FIG. VI. Aortic valves. The two cusps in the centre of the figure are practically replaced by solid calcareous masses. Where the original structure is left, it consists of thick fibrous tissue. The cusps are fused near their origin and fused portions are beginning to disappear. At the right and left corners of the picture, at the point of attachment of the cusps to the aortic wall, there is a fresh vegetation. A similar one was present a little higher up on the aortic wall on the left, where it has been cut away.

APPENDIX.

Condensed Notes on Cases represented by Figures.

Plate 6, Fig. I. W. B., aged 44. Pre-war a navy. No previous illnesses. Enlisted Sept. 1914, Norfolk. To France Aug. 1915, for four years on full duty except for short period for G.S.W. of tip of left middle finger. No illnesses while in the army or after demobilization in Feb. 1919. Resumed work as a navy and was all right till Aug. 1920, when he began to be short of breath. As this symptom increased he began to take one to two days in a week 'off work', but only gave up work in Jan. 1922. First seen at a medical board in March 1922. Big physique, complexion deeply cyanosed, marked venous engorgement, much dyspnoea, pulse 160. Abdomen distended with ascites, edge of liver at umbilicus, spleen huge. Fingers marked clubbing. Heart enlarged, loud to and fro bruits in aortic area. Wassermann positive. He died one month after admission. Aortic valves as in picture; mitral valves, a few fine calcareous vegetations scattered here and there on valve and chordae tendineae. Spleen, recent, old, and very remote infarcts.

Fig. II. P. M., aged 32. Pre-war a chemist's assistant, but also a cross-country runner. Only previous illness was an ulcerated throat thirteen years ago. Enlisted 1915. To Salonika 1916 for eighteen months, had dysentery for four days only. Returned home in 1917 to join O.T.C. Then had attacks of malarial fever. Transferred to Machine Gun Corps and went to France in August 1918, and went through to Germany, feeling quite fit. Demobilized Sept. 1919. Since discharge had had attacks of fever and sweating once every five weeks and had been short of breath, but kept on with his work until Feb. 1921, when he had an acute swelling of the right big toe, diagnosed as gout; this cleared up in three days. About the end of April 1921 he had a sudden pain in the right calf and a pulsating swelling appeared. This got smaller and was improving until the day before admission to hospital, when both pain and swelling increased. Admitted to hospital for the aneurysm, May 31, 1921. A tall, spare, muscular

man with some pallor of face, but marked pallor of skin of body. Fingers and toes advanced clubbing, spleen palpable and tender. *Heart*, heaving apex and arteries, Corrigan pulse, pistol-shot in femoral artery, to and fro aortic bruits. The whole of the right leg swollen hard and tender, especially over calf; right dorsalis pedis artery felt, but not posterior tibial behind inner malleolus. June 19, 1921, operation performed, femoral artery tied at bottom of Hunter's canal, the leg and foot became blanched and all distal pulsation ceased, but within one hour the leg regained its normal warmth and colour. Blood culture and Wassermann negative. He died Sept. 11, 1922. *Autopsy*: much the same as previous case.

Fig. III. W. R., aged 30. A clerk. No previous illnesses. Enlisted 1915 in Yeomanry, then transferred to Cyclists and then to infantry, no difficulty with training. To France, Feb. 1917. Wounded March 21, 1918, in left arm, back, and left foot. Wound of arm very septic; in hospital five months, and was discharged for paralysis (nerve suture) of this arm in Aug. 1918. Resumed clerical work, took plenty of exercise, and lately rowed a lot. In June 1920 he was noticed to be absent-minded, then complained of paresis of left hand which he ascribed to the old wound, and had some headache. On July 3, 1920, he had been canoeing on the river, and on his way back was heard to cry out that he had lost the use of his left arm, and then was seen to fall into the bottom of the boat. He was brought to the hospital, but never regained consciousness, and died at midnight. *Autopsy*: a tall, spare, muscular man, fingers clubbed. *Heart*, slightly enlarged; aortic valves as shown; a few sessile vegetations along the mitral valve. Spleen much enlarged but no infarcts, weighed 17 ozs. *Brain*, a large blood-clot on right ventricle with wide destruction of brain substance.

Plate 7, Figs. IV and V. E. A., aged 43. Army service twenty-five years; served in France, without wounds or illness, from 1914 to March 1918, when he was taken prisoner. While in Germany had dyspnoea on exertion and swelling of legs, not in hospital. Repatriated in Jan. 1919 and demobilized from army. Admitted to Norfolk and Norwich Hospital in July 1919 for intestinal obstruction; laparotomy performed, discharged in three weeks, no note being made of any cardiac disability. Readmitted October 19, 1919. A big man with healthy colour, advanced aortic disease, Corrigan pulse, clubbed fingers, and enlarged spleen, fine red petechiae on chest and abdomen. Also gave a history of Osler's nodes. Positive blood culture, streptococci in pairs and short chains. Wassermann negative. Four days later intestinal obstruction again occurred, laparotomy performed, much inflamed knuckle of gut liberated, but patient died two days later. During the anaesthetic the patient showed no sign of cardiac failure, did not require elevation of the head, and took the anaesthetic well. *Autopsy*: the freed gut was found to be gangrenous. Spleen, several massive, recent infarcts, also many others of older date. The valves are as shown.

Fig. VI. A. W., aged 25. Pre-war a thatcher, has never been on his sick club. History obscure. Enlisted A.I. in 1914 in the army, transferred to R.N. September 1915; there are no records, except of good conduct, until his discharge for 'epilepsy' in July 1919. After discharge he was eighteen months in the merchant service, but still had occasional fits, for which he was discharged in Jan. 1921. He was then trained as a motor mechanic and was seen at neurological boards for fits or neurasthenia until July 1922, when he showed cardio-vascular symptoms and was sent to a heart specialist, who admitted him at once to hospital. He had not been conscious of any disability until one month previously. On admission, a man of fine physique, ruddy colour but cyanosed. Skin of the body pale and cyanosed. Finger and toes extremely clubbed, spleen and liver much enlarged, ascites present. *Heart*, much enlarged, loud to and fro bruits in aortic area; oedema of back, legs, and scrotum. Blood culture negative. Wassermann reaction positive. He died on Sept. 5, 1922. *Autopsy*: aortic valves as shown; mitral valves, no vegetation. Spleen very large, but showed only one fibrous scar of an old infarct at the lower pole. Kidneys showed scars of old infarcts. N.B.—This case is not included in the figures already given.

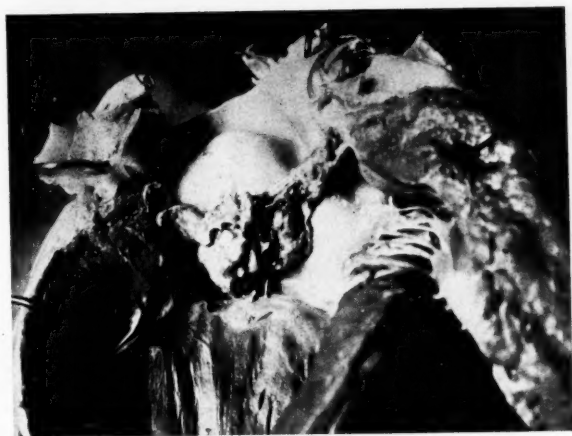


FIG. I



FIG. II



FIG. III



FIG. IV



FIG. V



FIG. VI

THE FIXATION OF THE KIDNEY

By A. H. SOUTHAM

With Plates 8-10

Introductory Remarks.

THE work described in this thesis was undertaken to try and obtain a clear and concise account of the fascial relations and attachments of the human kidney. The kidney has no special ligaments, like the liver, to retain it in position, and different accounts have been given as to how this is effected. Prolapse and displacement of the organ are by no means uncommon, and so this subject appeared worthy of further investigation.

The task was carried out in the Anatomical Department of the University of Manchester, and I desire to express my thanks to Professor J. S. B. Stopford for his kind advice and many valuable suggestions and the liberal supply of material he has placed at my disposal. In addition, clinical observations have been made in the wards and Out-patient Department of the Manchester Royal Infirmary.

The literature on the fascial attachments of the kidney is peculiarly scanty in the English works, and no two authorities appear to agree in their descriptions of this structure, some even doubting its presence as a definite entity. It is on account of this uncertainty on the subject that this investigation was undertaken.

Six fetuses and seven adult bodies have been examined and cut in sections with a band-saw to enable a study of the perirenal fascia to be obtained. Over forty bodies have been examined in the dissecting and post-mortem rooms, and plaster casts made of the renal fossae in a number of these subjects.

Histological sections have been prepared to show the character of the tissue which connects and surrounds the kidneys, and micro-photographs are reproduced of a few of these sections. Diagrams and a number of tracings of the renal fossae are also included. Though many structures take a secondary part in supporting the kidneys, it is probably to the perirenal fascia and the maintenance of intra-abdominal tension that the chief importance must be attached. The fact that prolapse of the kidney is so often seen and is commoner among women has impelled me to endeavour to discover what factors are responsible for producing displacement more frequently in one sex than the other. Although the original plan was only to investigate the fascial attachments of the kidney, the importance of the clinical aspect of the subject led me to include it also in my observations.

1. *Historical Introduction.*

The knowledge of diseases of the kidneys possessed by the ancients was limited, as far as appears from the writings of Hippocrates, to injuries and supuration of the kidney and the existence of renal calculi. The earliest references in medical literature on the subject of movable kidney are found in the writings of Francis Pedemontanus in 1581, and of Riolan in 1682, whilst Mesue of Venice wrote a chapter on this subject in 1497. Riolan observes that the normal condition of the kidney is a fixed one in the flank, but that under certain conditions it becomes movable, and that stones or growths in the kidney especially favour the loosening. Rayer, in 1846, in his work *Diseases of the Kidney*, reported seven cases of mobile kidney, which he thoroughly studied, not only from an anatomical but from the clinical standpoints of diagnosis, symptomatology, and treatment. He noted the condition was commoner in females than males, and that it affected more frequently the right kidney. He also noted that pregnancy and heavy lifting were contributory causes, and that the patients were usually thin and hypochondriacal. Finally, he stated that in some cases bandages gave relief. In 1864 Dietl described the crises found in certain cases of mobile kidney and gave birth to the term 'Dietl's crises'.

The first operation ever performed for movable kidney was by Martin of Berlin in 1878, when he carried out nephrectomy in two cases. This operation is never performed at the present day for this condition. Suspension of the organ was first carried out by Hahn of Berlin in 1881, and his lead has been followed by many operators, and a vast number of operations have been devised to secure fixation of the kidney. Glénard, in his writings of 1885 and 1900, maintained that movable kidney was not a condition in itself, but part of a general enteroptosis, due to a congenital weakness of the supporting structures of the abdominal viscera. Landau, in 1881, had maintained that the kidney was normally fixed and any degree of mobility was abnormal. This we now know is not true, as the organ normally moves with respiration.

More recently, Fitz, Dell, Treves, Goelet, Suckling, Billington, Newman, Edebohls, and Lane have added to the literature on this subject, whilst Sir Henry Morris and Sir William Roberts contributed valuable additions to our knowledge. Up to 1901 Sir Henry Morris had performed 98 operations of nephropexy with one fatal result.

Sappey and Zuckerkandl in 1883 described a thickening of the connective tissue on the posterior surface of the fat capsule of the kidney which they called the fascia retrorenal. Gerota in 1895 described a layer on the anterior surface which he called the fascia prerenal. The fascia is more marked on the left side, and this fact was first demonstrated by Toldt. Apart from this, little original work on the fascial attachments of the kidney appears to have been done.

2. *Gross Anatomy.*

The kidneys lie in the lumbar region on either side of the vertebral column. Each kidney occupies the upper third of the lumbar fossa, a space which is bounded behind by the muscles of the loin and back, in front by the peritoneum, above by the diaphragm, and below by the ilium. The kidney extends from the upper margin of the twelfth rib to the lower margin of the second lumbar vertebra. The kidneys are situated entirely behind the peritoneum, and the right kidney lies about a finger's breadth lower than the left. This is said to be due to the fossa on the right side being less capacious on account of the presence of the liver and an inclination of the vertebral bodies to that side.

The peritoneal relations are somewhat different on the two sides. On the right side the peritoneum passes from the liver to the anterior surface of the kidney, the lower third of the kidney is not covered by peritoneum. The area of the left kidney covered by peritoneum is far less than that of the right kidney.

The upper third of the left kidney is related to the stomach, whilst the pancreas crosses its middle third; the lower third is covered by peritoneum and related to coils of small gut, the outer border being related to the spleen above and the colon below.

The upper two-thirds of the right kidney is covered by the under surface of the liver, the lower third by the hepatic flexure of the colon. The inner border is related to the duodenum.

The posterior surfaces of the ascending and descending colon are not covered by peritoneum, and hence the gut comes into close relation with the perirenal fascia. The suprarenal gland rests upon the upper pole of the kidney, whilst posteriorly the kidney lies upon the quadratus lumborum and psoas muscles, the diaphragm, and the transversalis aponeurosis.

3. *The Renal Fossae.*

If the lumbar regions be examined from behind it will be seen that there is a difference in outline in the two sexes. In the female the lumbar region broadens out below and has the appearance of a cone with the apex above, whilst in the male it is more cylindrical in shape and tends to become narrower below. This is due to the increased breadth of the female pelvis, and in some cases an acquired narrowness of the lower costal margin. In the male the lower ribs are more horizontal and the chest has a greater width, whilst the measurement across the iliac crest is relatively small. In the female the intercrystal diameter of the body may be greater than the transverse diameter of the lower thorax by $2\frac{1}{2}$ centimetres. Now if the fossae in which the kidneys lie be inspected it will be seen that they also differ in shape in the two sexes. In males they are distinctly pear-shaped and become narrower below, whilst in females they are relatively narrow above and broaden out below or are cylindrical in shape. Further, a comparison of the fossae on opposite sides of the body shows the right

renal recess is usually a little larger than that on the left side. To study the shape and capacity of these fossae I have examined these recesses in over forty bodies, and to obtain a clearer idea of their conformation I have made a series of twenty-four plaster casts of the renal recesses. Plaster casts of the fossae confirm the differences in the sexes already described.

The male fossae are always distinctly pear-shaped with the narrow end below, whilst in the female they are cylindrical or may be slightly wider at the bottom. Tracings of these fossae are shown to illustrate their differences in outline (Figs. 1-8).

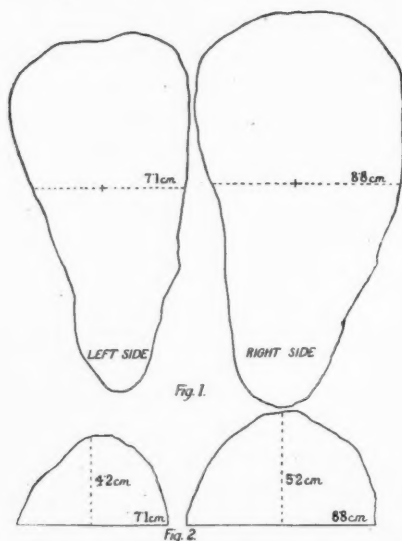


FIG. 1. Outline of casts to show shape of renal fossae in male subject. Fossae are pear-shaped with narrow end below. Measurements at level of 1st lumbar vertebra show right fossa is larger in transverse diameter.

FIG. 2. Transverse sections of casts shown in Fig. 1 at level of 1st lumbar vertebra. The right fossa is seen to be deeper than the left.

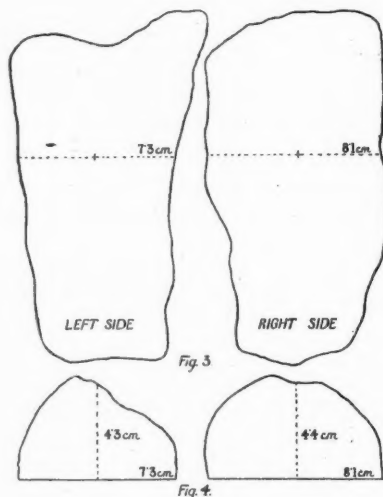


FIG. 3. Outline of casts to show shape of renal fossae in female subject. Fossae are open below. Measurements at level of 1st lumbar vertebra show right fossa is larger in transverse diameter.

FIG. 4. Transverse sections of casts shown in Fig. 3 at level of 1st lumbar vertebra. The two fossae are of equal depth.

In most cases the fossa of the right side is more capacious than that on the left. To demonstrate this fact to better advantage, transverse sections of the casts were cut with a band-saw at the level of the first lumbar vertebra (which point was previously marked on the cast whilst in the body).

In the male the right recess is appreciably larger than the left; the average measurement in my plaster casts shows the right side is about two centimetres broader than the left at the level of the first lumbar vertebra. The fossa of the right side is deeper than that of the opposite side by an amount of rather under one centimetre at the same level (Figs. 1, 2, 5, and 6).

In the female the two fossae are often of equal size, though when this is not

the case the right side is larger to the extent of one centimetre, rarely more. As to the depth, they vary very little, usually being the same in this respect: in only one case was the right side half a centimetre shallower than the left (Figs. 3, 4, 7, and 8). Tracings of the plaster casts are reproduced to illustrate their outline, and the following variations are noted:

1. In the male the renal recess is distinctly pear-shaped in outline, with the narrower end below.
2. In the female their shape is cylindrical and may even widen out below.
3. In the male the right recess is larger and deeper than the left.
4. In females the recesses are usually equal in size and depth, though the right side may be a little larger in transverse diameter.

The fossa is lined by the lumbar muscles, and its outline is also to some extent dependent on the development and tone of these muscles. Where wasting or loss of tonus occurs the outline of the fossa will be altered, tending to increase its capacity. Further, the fossa is padded with a layer of fat, derived from the sub-peritoneal fatty tissue. This pararenal fat is best developed at the lower part of the renal recess and forms a shelf for the inferior pole of the kidney to rest on. Should this fat disappear in disease, the shape of the fossa will again be modified.

Mansell Moullin has described a rotation of the vertebrae to the right, causing a shallowness of the recess as a result. I have not observed this rotation in any of the subjects I have examined.

The increased capacity on the right appears to depend chiefly on the presence of the liver. This organ occupies the upper part of the right sub-diaphragmatic space and causes an increase in the right paravertebral recess. Also the direction of the eleventh and twelfth ribs determines the shape of these recesses to some extent—perhaps the increased size in the male may depend on greater activity of the muscles and arms of this side.

The cylindrical shape of the fossae in females is accounted for by the expansion of the iliac crests outwards, whereby the transverse measurement here is greater than that of the lower thorax by $2\frac{1}{2}$ centimetres.

In twenty female subjects I have examined, this increase in the intercristal measurement is found to be almost constant.

In males the reverse is found to be the case; the measurement round the lower thorax shows an increase of 2 or $2\frac{1}{2}$ centimetres over the pelvic diameter.

In children the pelvic measurement is less than that of the chest, and hence we find a possible cause why renal prolapse is found in adults and usually in the female sex.

4. *Development and Comparative Anatomy.*

The kidney arises as a tubular diverticulum from the Wolffian duct and is first seen during the fourth week of development. At first the organ is distinctly lobulated and shows this lobulation at birth, and sometimes even persists up

to adult life, where evidence of its original subdivision can be traced. The position of the kidney in its fossa is very different in the adult to what is found in the new-born. It is much smaller in proportion in the adult, and there is a difference in the position of its transverse axis. In the new-born the axis is almost straight laterally, in the adult it leans backwards in a varying angle depending on the depth of the paravertebral fossa, into which the organ swings back round an axis represented by the aorta. Fixed misplacements of the kidney are usually congenital, movable displacements being acquired. Fixed misplacements occur about 1 in 1,000 bodies (Morris), and when only one kidney is misplaced it is usually the left, and associated with this the descending colon may be found across the mid-line on the right side.

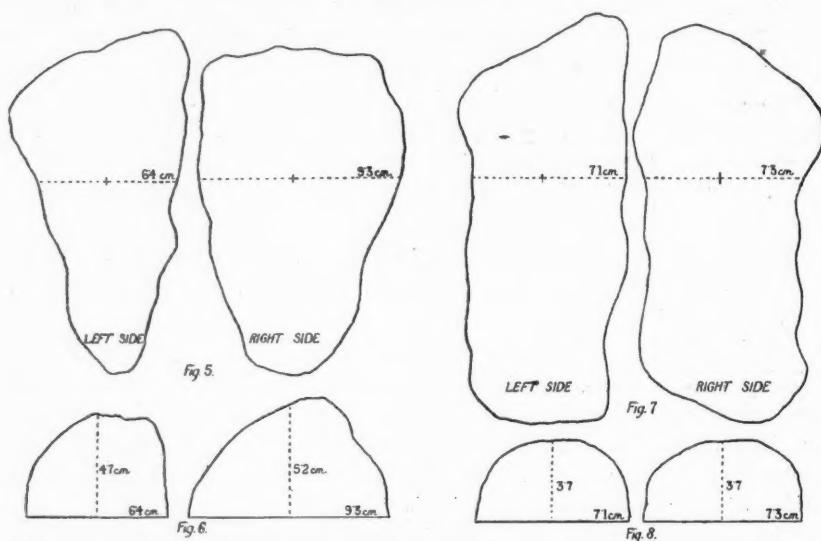


FIG. 5. Outline of casts to show shape of renal fossae in male subject. The fossae are pear-shaped, and the right fossa is the larger.

FIG. 6. Transverse sections of casts shown in Fig. 5 at 1st lumbar level. The right fossa is deeper than the left.

FIG. 7. Outline of casts to show shape of renal fossae in female subject. The fossae are open and the right tends to widen out below.

FIG. 8. Transverse sections of casts shown in Fig. 7. Both fossae are shallow and of equal depth.

When the kidneys are abnormal in shape or position an abnormal blood supply is very common.

Accessory Renal Arteries. Abnormalities of the renal arteries are more common than those of any other artery. Thane states irregularities occur as frequently as 25 per cent., and the commonest is an additional vessel present in about 20 per cent. of bodies. According to Macalister irregularities are present in three out of seven bodies, the accessory vessel most commonly arising from the aorta. He found the commonest was an accessory right aortic branch, next one additional left aortic branch. Arthur Thomson states irregularities were found in 25.6 per cent., and in 10.9 per cent. one accessory aortic branch was

found. According to Young and Thompson, accessory renal arteries are commonly found with an arrested development of the kidney.

Originally the renal arteries are multiple, most of them disappear by fusion and leave a single renal artery on each side.

Multiple renal arteries represent a primitive condition, and when present the kidney often shows lobulation or is in some abnormal position, whilst sometimes the kidneys may be united and form a horseshoe kidney.

Comparative anatomy and embryology at once suggest solutions of these multiplications of arteries. In the lower animals the renal arteries are multiple. The researches of His showed that the aortic branches supplying the intermediate cell-mass are multiple, and Broman showed these vessels are primarily arranged segmentally. The occurrence of supernumerary renal arteries may be a reversion to the multiple condition. This multiplication of arteries is of interest when considered in relation to the fixation of the kidney. Morris states that additional arteries are commonest on the left side. When present they may act as additional support for the organ.

Some consider an accessory artery is an important factor in the production of hydronephrosis and raise the question whether such a vessel can obstruct the ureter unless the kidney is unduly mobile. My investigations suggest that additional renal arteries are seldom found associated with mobile kidney. Bevers, in a case of this nature, subsequently referred to, found the kidney was not unduly mobile.

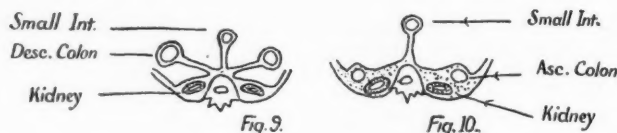
Floating kidney. The term 'floating kidney' is applied to the organ when it is surrounded by peritoneum and possesses a mesonephron. This is a congenital condition and rarely seen. Cases have been recorded by Newman, Roger, and Priestley.

Comparative Anatomy.

A study of comparative anatomy and the process of evolution whereby man and the higher apes adopt the erect posture throws interesting light on the position and the fixation of the kidney.

If the development of the renal organs is followed it is seen that originally they were distributed over the whole length of the head and the body. By degrees, as their function became more specialized, they became concentrated together, until they formed a pair of organs buried in two deep and narrow recesses, on either side of the spine, in a position of great safety. The kidneys here rest upon a horizontal shelf of fascia which lies upon the peritoneal viscera, slight to and fro movements taking place on this, due to the action of the diaphragm. Such is the condition found in the quadruped animals. With the assumption of the erect attitude a great proportion of their security became lost. The supporting structures now lie in front and not below, as in the quadruped, and the lumbar recesses have become broader instead of deeper. The pelvis of the female has become wider, and so the lower ends of the renal fossae are more

open. Thus the security of position of the kidneys is gone, and this accounts for the frequency of mobile kidney found in man due to lack of adaptation to the upright position. It therefore becomes apparent that the adoption of the plantigrade mode of progression in man has resulted in a natural tendency to prolapse of the kidney. The effect of the erect posture has been to remove some of the natural supports of the kidney, and the widening of the pelvis—especially seen in the female—has led to a broadening out of the paravertebral fossae and a natural susceptibility to descent of the kidney. In any consideration of the mode of fixation of the kidney it is necessary to recall the development and evolution of that part of the gut which is related to the kidney.



FIGS. 9 and 10. Diagrams of transverse sections through abdomen, to show peritoneal arrangement before (Fig. 9) and after (Fig. 10) fixation of the colon has taken place.

In early intra-uterine life the mid-gut is suspended from the spine by a single dorsal mesentery. About the fourth or fifth month this mid-gut loop undergoes a rotation round its axis and the caecum comes to lie on the right side. At this period the mesocolon is free and has two layers of mesentery, and the colon is free in its entire length (Fig. 9). The kidney at this stage is covered in its lower part by parietal peritoneum. Then the primitive mesenteries of the ascending and descending colon disappear and the colon comes back against the posterior parietal peritoneum, and the two layers of the mesocolon and that covering the posterior portion of the colon fuse with the parietal peritoneum. This produces an appearance as if the parietal peritoneum were reflected over the lateral border of the colon (Fig. 10). The colon thus becomes fixed in position. The name 'fascia of Toldt' has been given to that part of the anterior layer of the perirenal fascia which is found where the colon is related to the kidney. It is here reinforced by the fusion of these three layers of peritoneum. It covers a considerable area on the front of the left kidney, but only a small area over the lower pole of the right kidney. I have found in dissections that the perirenal layer covering the anterior surface of the left kidney is thicker and better developed, and this is of interest when we consider that mobile kidney on the left side is not common and the importance that is attached to the perirenal fascia in the fixation of the organ. The explanation of this phase of intestinal development is made clear by a study of comparative anatomy.

On examination of a series of mammalian types in which the mid-gut loop rotates closely analogous to that in man, there is a lack of this peritoneal fusion and the original mobility of the colon persists in the pronograde animals. The dog and the monkey have a colon that is completely mobile. As we ascend to the higher anthropoids we find the fixation of the colon progresses with the

adoption of the erect posture and approaches that type found in man. So fixation of the colon is evolved as an adaptation to the erect posture.

Now mobility of the descending colon is not common in man, but mobility of the ascending colon and caecum is found in approximately 20 per cent. of all individuals. This figure is of interest, as it closely corresponds with the frequency of abnormally mobile kidney which is found present on the right side in 22.8 per cent. of living women (analysis of figures of Edebohls, Glénard, Goelet, and Hahn).

Mobile kidney is only found in 2 per cent. of all men, and visceroptosis, again, is seldom present in the male sex.

So it appears that the fixation of the colon, which arose in the course of evolution, may be associated with the fixation of the kidney by the support it affords to the kidney, especially of the left side, through the fascia of Toldt, and the close relation of the colon itself to the margin of the organ.

5. *The Perirenal Fascia.*

This is the fascial envelope which surrounds the kidney, and is quite distinct from the fibrous capsule of the kidney which closely invests the organ and lines the renal sinus. To enable a clear conception to be obtained of this structure I have carried out a study of its arrangement by making a series of transverse and vertical sections of the body. This has allowed me to form an accurate idea of its disposition, and all the findings here described have been confirmed repeatedly. The perirenal fascia—sometimes called the fascia renalis, fascia propria, tunica fibrosa, capsule of Gerota, Kustner, or Zuckerkandl—consists of a thin sheath of fascia which completely surrounds the kidney and suprarenal body. The sheath is separated from the kidney by a layer of fat within which the kidney is embedded.

When examined in a transverse section of the body it is seen to consist of two layers, an anterior and a posterior layer.

The anterior, perirenal layer or fascia of Toldt is a thin fibrous membrane which lies between the peritoneum and the anterior surface of the kidney. Where it comes into relation with the peritoneum the two layers are closely blended together; where, however, the peritoneum is absent, it is related to the neighbouring viscera. It is generally stated that at the inner border of the kidney this layer passes in front of the renal vessels, great vessels of the abdomen, and the vertebral column to join with the corresponding layer of the opposite side, and thus there is a communication of the two fascial sheaths across the mid-line. Such is the description given by Gerota, Piersol, Morris, Cunningham, and other authorities. This arrangement has been questioned by Poirier, and to settle this point I have examined fifteen transverse sections of the body. As a result I have been unable to establish any connexion across the mid-line. The fascia can be traced as far as the pancreas and to the root of the mesentery, and there becomes lost in the connective tissue elements present in this situation.

This is the true anatomic arrangement and accords with the scheme of Poirier, who further points out that perirenal suppuration of one side has never been found to spread across to the tissues of the opposite side, as might be expected if a communication across the mid-line was present.

The posterior layer or fascia of Zuckerkandl is a thicker membrane and separates the kidney from the fascia overlying the lumbar muscles. At the inner border of the kidney this layer reaches to the vertebral column and becomes firmly attached to the bodies of the vertebrae in front of the origin of the psoas muscle. This layer does not extend beyond that point to cross the mid-line to the opposite side (Fig. 11). Morris, in his description of the posterior layer, states that it becomes lost in the connective tissue over the vertebral column; Piersol, however, says it is attached to the spine, and most writers agree on this point. Cunningham states that the sheath is open internally and the walls remain distinct, this description being generally accepted. I have, however, found in repeated dissections that the arrangement differs both above

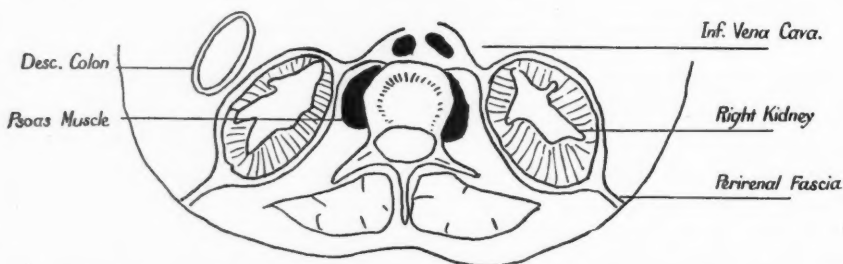


FIG. 11. Diagram to show attachments and relationships of perirenal fascia in transverse section of abdomen. The band-like formations at the inner and outer poles of the kidney are demonstrated. This section is taken just above the level of the hilum of the kidney.

and below the hilum of the kidney. Above the hilum these two layers come together at the inner border of the kidney, being separated only by a deposit of fat; the posterior layer then becomes attached to the spinal column and the anterior ends as already described. At the level of the hilum they are kept apart by the renal vessels, whilst, below, the ureter lies between them as it passes down to the pelvis. To recapitulate, the posterior layer of perirenal fascia at the inner border of the kidney is attached to the vertebral column, whilst the anterior joins with the posterior layer above the hilum; below this point the two layers are separated by the renal vessels and ureter. The anterior layer ultimately becomes lost in the fascia around the great vessels and the pancreas.

At the outer border of the kidney I find that the two layers of fascia come together and join each other, forming a well-marked band, which passes out behind the peritoneum to join with the transversalis fascia. This band appears to be constantly present in both the foetus and adult, and is easily seen on transverse section. It forms an important means of fixation of the kidney and does not appear to have been previously described. Photographs of sections of the foetal

and adult body are shown in which this band-like structure is well seen (Plate 8, Figs. a and b).

Other accounts of the arrangement of the fascia at the outer border of the kidney are singularly incomplete. Cunningham states that the walls of the sheath come into contact and are connected with the retroperitoneal tissue. Thomson Walker merely states that the perirenal fascia appears between the transversalis fascia and the peritoneum and divides into two layers, whilst Kelly and Burnam find the two layers unite at varying distances and then pass forward under the peritoneum. Morris says it ends indistinguishably in the sub-peritoneal fascia, and Poirier states that the fascia is closed at the outer side and mentions no specific attachments.

When examined in vertical section the arrangement of the fascia is found to be as follows: The anterior and posterior layers, after enclosing the kidney and suprarenal body in one compartment, join together at the upper pole of the suprarenal and pass up as a single strong band to unite with the tendinous area

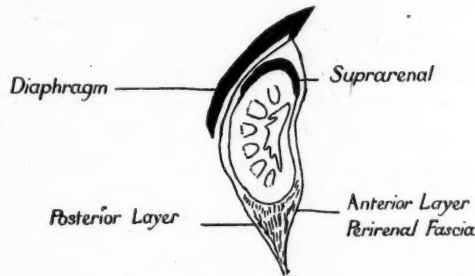


FIG. 12. Diagram of vertical section through kidney to show the arrangement of the perirenal fascia and its attachments to the diaphragm at the upper pole of the kidney above the suprarenal.

of the diaphragm. There is thus formed a strong suspensory band for the kidney when the body is in the erect posture (Fig. 12). Some writers, including Sappey, Billington, Knight, and von Bergmann, state that the kidney and suprarenal are separated from each other by a layer of the perirenal fascia intervening, and that each organ lies in a separate compartment. I have not found this to be the case in a single specimen examined; the suprarenal is attached to the upper pole of the kidney by fibrous tissue strands which become more marked as age advances.

In the foetus the suprarenal is of relatively larger size than in the adult, and its connexion with the kidney is firmer. When the kidney prolapses in the adult the suprarenal is left behind, being held *in situ* by its fascial attachments and vessels and nerves, as will be described in a later section.

At the lower pole of the kidney the anterior and posterior layers of fascia do not actually fuse. They are held together by fine strands of fibrous tissue which are well marked just below the kidney.

The anterior layer closely follows and ultimately blends with the perito-

neum, whilst the posterior layer becomes fused with and disappears in the fascia over the iliacus muscle. This corresponds to the description usually given in that situation.

The arrangement of the fascia in vertical section is well shown in the photograph of an adult body given on Plate 9.

On the left side the anterior layer of the perirenal fascia is thicker than that of the right side; this is due to the fusion of the three layers of peritoneum with the fascia which occurs in the course of development and fixation of the colon.

To recapitulate: The kidney is enclosed with the suprarenal capsule in a fascial envelope composed of a strong posterior and a thinner anterior layer. This fascial sheath is firmly attached to surrounding structures. Above, the layers unite and form a suspensory band which is attached to the diaphragm, whilst at the inner and outer poles of the kidney the two layers again join and are attached to the vertebral column and the transversalis fascia. In front and behind it is attached by fine connective tissue strands to the peritoneum and the lumbar fascia. The kidney, surrounded by the perirenal fat, is attached within this sheath by connective tissue elements which are better developed at the lower pole of the kidney (Plate 10, Fig. b).

This fascial sheath is closed above and at the outer side by the fusion of its anterior and posterior layers. At the inner border the layers come together but do not fuse, whilst below they can be easily separated. There is thus a potential channel below ready for the kidney to descend in should prolapse of the organ occur.

Plate 10, Fig. a, shows a micro-photograph of the perirenal fascia, which is seen to be composed of strands of fibrous tissue.

Plate 10, Fig. b is a micro-photograph which shows the capsule of the kidney and the perirenal fascia; passing between these two structures is one of the strands of fibrous tissue which supports the kidney within its fascial sheath.

6. *The Perirenal Fat.*

The perirenal fat or fatty capsule of the kidney I have again investigated by means of sections of the body at different levels and in different planes. The perirenal fat surrounds the kidney and suprarenal body, and is enclosed within the perirenal fascia. This fat I have found to be constantly present, though it varies with the age, sex, and different levels of the kidney. Morris, Sappey, Walker, and von Bergmann say that no fat is present in the foetus and that it does not appear till about the tenth year. In the six foetuses which I have examined fat was present in every case (Plate 8, Fig. b). In these specimens there was a well-marked deposit of fat at the inner and outer poles of the kidney, particularly well marked at the level of the hilum. There was a scanty deposit on the posterior aspect and at the lower pole, whilst it was better marked above around the suprarenal.

The fat I have found increases in amount up to adult age, whilst in old

subjects it becomes less abundant. In female subjects the fat is present in a proportionately greater amount than in males.

In the adult it may be absent on the anterior surface of the kidney, though in some cases I found a very thin layer present. On the posterior aspect it is found in considerable thickness, a fact which is well recognized in surgical work on the kidney. At the inner and outer borders a well-marked deposit of fat is found between the layers of the perirenal fascia, and particularly around the vessels at the hilum, whilst at the upper and lower poles fat is found in considerable amount and forms a bed for the lower pole of the kidney to rest in. Where the colon comes into relation with the kidney a deposit of fat fills in the intervening space.

The perirenal fat forms a soft bed in which the kidney lies. It acts as a cushion to protect the kidney from injury and to allow sudden changes of intra-abdominal pressure to occur without affecting the organ. Around the vessels at the hilum it enables changes in the volume of the vessels to take place when an increased blood supply is required. Behind, it acts as a buffer between the kidney and the rigid costal margin. Below, it forms a bed within which the kidney can descend during normal respiration. The fat is traversed by thin fibrous tissue strands which pass from the kidney fibrous capsule to the inner side of the perirenal fascia. These fibres are more numerous and better developed at the lower pole of the kidney and take a part in the fixation of the gland (Plate 10, Fig. b). The more fat there is present within the perirenal sheath the more firmly will the kidney be packed in position. The amount of fat must assist in restraining mobility of the organ. If the fat disappears rapidly due to wasting disease, and the fibrous bands do not contract at the same time, the kidney may acquire an abnormal degree of mobility within its fascial sheath, a condition which is found in life sometimes. If, however, the disappearance of fat is a slow process, and the fibrous strands shorten at the same time, no excessive range of mobility need take place. Again, if these strands are poorly developed or abnormally stretched, the fixity of the kidney will be impaired.

The Pararenal Fat.

Behind the posterior layer of the perirenal fascia and in front of the transversalis fascia there is found a potential space. In this space there is usually a deposit of fat, namely the pararenal fat. This fat was always present in the adult bodies I examined, and it increases in amount towards the lower pole of the kidney and forms a pad on which the kidney rests just above the iliac crest. It is quite distinct from the perirenal fat and appears to be merely a specialized portion of the retroperitoneal fat. Gerota describes this layer, but Poirier is doubtful as to its constancy. I was able to show its presence in all the adult bodies. It is, I think, not unlikely that cases of perinephric abscess, the aetiology of which is often open to doubt, may arise in this pararenal fat. These abscesses frequently occur without any renal symptoms, and in cases that require draining

I have found the pus to be superficial and appear not to involve the perirenal fat. These abscesses are generally localized and do not track down the pelvis, as might occur if arising within the perirenal sheath.

7. *The Renal Supports.*

Having described the fascial connexions and the fatty capsule of the kidney, it will now be convenient to consider those structures which may be of importance in fixing the kidney in its normal position in the renal fossa.

The kidney, unlike the liver and the uterus, has no special ligaments for keeping it in place, and, being liable to displacement, its means of support are of considerable importance.

Probably certain anatomical structures and forces all take their part in this process, and these can conveniently be described under the following headings: (a) The perirenal fascia. (b) The perirenal fat. (c) The suprarenal gland. (d) The vascular pedicle. (e) Intra-abdominal tension. (f) The peritoneal relations.

(a) *The perirenal fascia.* This fascia has already been described in considerable detail (see Figs. 11 and 12, also Plates 8-10).

The perirenal fascia forms a well-marked sheath for the kidney and has important attachments to surrounding structures. Above it is fixed to the diaphragm, to the inner side to the vertebral column, whilst to the outer side it is attached to the transversalis fascia. In addition it is adherent to the peritoneum and lumbar fascia. Below, the sheath is open and allows for the descent of the kidney. The kidney itself is attached within its sheath by strands of fibrous tissue. Under normal conditions the kidney moves in a downward direction during respiratory movements and when the body assumes the erect posture. Under certain abnormal conditions, which are yet to be described, the kidney may attain an increased degree of mobility. It then prolapses within the sheath and is further drawn inwards, towards the mid-line, by the attachments of the renal artery and vein. It will be shown that all the other attachments of the kidney are merely contributory: they can be divided or removed without affecting the fixity of the organ to any material extent so long as the fascial attachments remain intact. A point of clinical interest is that if the normally placed kidney be explored for stone or other reason it ascends and descends with each movement of the diaphragm. If the lower pole be grasped it can only with great difficulty be kept from ascending with each expiration. This appears due to the upper attachments of the perirenal fascia to the diaphragm and the kidney, which is a strong band fixing the kidney to the diaphragm, and results in the kidney following the respiratory movements of the diaphragm.

This fascia, then, through its connexion with neighbouring structures and its attachments to the kidneys, itself evidently takes a share in the fixation of the organ. The suprarenal gives little support to the kidney in the adult, and the renal vessels may be divided and the peritoneum and surrounding organs

removed, yet the kidney is held in position by the perirenal fascia and its attachments.

(b) *The perirenal fat.* This consists of soft lobulated fat surrounding the kidney and enclosed within the perirenal fascia. Through it pass delicate strands of connective tissue between the capsule of the kidney and the perirenal fascia. Under normal conditions this fat moves with the kidney on respiration, as can easily be observed on the operating table. If the fatty capsule is large and loose the kidney may move within it. This fat appears to adapt the kidney to the space within which it lies and to protect it against sudden injury or changes of pressure. It seems reasonable to assume that if the fat disappears the kidney may acquire an abnormal degree of mobility within its capsule. Keen finds general emaciation favours mobility of the kidney, and Morris considers deficiency of fat to be one of the chief causes of renal mobility. On this assumption it has been suggested that by increasing the fat in a person with renal prolapse the condition could be improved. But there are other more important factors present in mobile kidney, and the amount of fat is of little importance, and I have seen it present in such cases in excessive amount. Little fat is found present in children as compared to adults, and mobile kidney is rare in young persons. Hence we must assume that it is not of great importance in supporting the kidney, acting rather as a protection to the organ and packing around it.

(c) *The suprarenal gland.* This organ is held in position by its attachment to the diaphragm through the perirenal fascia. It also has a rich arterial and nervous supply which give it further fixation, and is closely related to the liver, spleen, and pancreas, to all of which it has connective tissue attachments.

It lies at the upper pole of the kidney, and when prolapse of the kidney occurs in an adult the suprarenal gland does not follow the kidney in its descent. The suprarenal is attached to the upper pole of the kidney by weak strands of fibrous tissue which are easily separable, but being firmly attached to the diaphragm it does not accompany the kidney when that organ is mobile. In surgical operations on the kidney the suprarenal gland is seldom seen, being too firmly fixed in position.

We must conclude that this organ gives little support to the kidney. In the child, however, affairs are totally different. The suprarenal is firmly attached to the kidney and it requires considerable force to separate the two organs. Gerota showed that if all the other renal supports were divided in a child the suprarenal was able to hold the kidney in position.

The development of the suprarenal is quite distinct from that of the kidney; it is unaffected by those conditions which influence the kidney, and so takes little part in the fixation of that organ.

(d) *The vascular pedicle.* The renal vessels run in a horizontal direction to reach the kidney. In cases of mobile kidney the vessels may be lengthened to a considerable extent. Billington records a case where the renal pedicle was six inches in length. Is the increased length the cause or the effect of mobile kidney? The normal respiratory movements of the kidney are in an up and down direction;

if the renal vessels influenced these movements the kidney would tend to be drawn towards the mid-line in the arc of a circle. Only in cases of excessive mobility does this occur, and rarely the kidney has been found to slip over the spinal column. Poirier records a case where in a patient with mobile kidney the renal artery was considerably lengthened, whilst the vein, being more resistant, was not affected. Legueu showed that after division of the renal vessels in the cadaver the fixity of the organ is not affected, and I have myself found this to be the case. It can be shown in the dead body that kidneys with long pedicles are not more mobile than those with short pedicles, and this is the general opinion of surgeons. It is certainly a fact that the left renal artery is two centimetres shorter than the right, and this has been considered a reason why the left kidney is less often prolapsed than the right. Abnormal renal vessels, rarely found in association with movable kidney, are generally present on the left side; perhaps they may serve to limit excessive mobility when present. It appears probable that, under normal conditions, the renal vessels afford little support to the kidney; only when the organ is prolapsed to an excessive degree do they exert any restraining influence on the movements of the kidney.

(e) *Intra-abdominal tension.* In considering the main factors which retain the kidney in its normal position in the loin, the question of the maintenance of intra-abdominal tension by the musculature of the abdominal wall must be carefully investigated.

The kidney is exposed to constant pressure by the diaphragm on the one hand, and the muscles of the abdominal wall on the other. The inspiratory descent of the kidney depends entirely on the contraction of the diaphragm. Does a loss of muscle tonus lead to loss of renal fixation? Volkoff and Delitsin have shown the importance of the abdominal tension in supporting the kidneys. After dividing the abdominal muscles in the cadaver, descent of the kidney occurs when the body is placed in the erect posture, and this reaches its maximum when the peritoneum is opened and the abdominal pressure falls to zero. It is shown subsequently that mobile kidney is far commoner among females and in those with a lax abdominal wall. Any condition which leads to loss of muscular tone in the abdominal wall may result in visceroptosis and prolapse of the kidneys. The greater frequency of this condition in females depends on the fact that in males the musculature is better developed. Though pregnancy in itself is not a direct cause of prolapse, where a proper convalescence is conducted, yet in the poorer class of patient, where pregnancies are oft and rapidly repeated and the patient assumes the erect position too early, the muscles are lax and flabby and may result in permanent loss of tone and a fall in intra-abdominal tension. Further, males are less liable to these sudden changes in intra-abdominal tension, and by their occupation and mode of life tend to increase their muscular tone. Women lead less active lives and are naturally less well developed, whilst pregnancy, perhaps tight-lacing, and a generally sedentary life tend to reduce muscle tonus and produce a lowering of intra-abdominal pressure. Further, any conditions which produce abnormal distension of the abdomen, such as large ovarian

tumours or collections of ascitic fluids, tend to dislocate neighbouring organs and so stretch and strain the normal connexions which exist between them and the kidneys. Since Rayer's day a relaxed abdominal wall has been considered effective in producing abnormal mobility of the kidney, and in practically all the cases of this nature I have had the opportunity of examining the woman has shown a lack of tone of the abdominal muscles.

It appears that the intra-abdominal pressure through the upward thrust of the more mobile viscera is of considerable importance in supporting the kidneys. The tone of the abdominal muscles helps to retain the organs in position and is an important factor in this respect.

This, perhaps, would account for the fact that descent of the kidney, though not uncommon in females, is seldom found in males, as in the latter sex muscular development is better developed and maintained, and the causes which lead to loss of tonicity in women are not observed in males.

Mobile kidney is rare in children, except as a congenital defect, and again in children the abdominal musculature is usually well maintained.

(f) *Peritoneal attachments.* The parietal peritoneum covers a considerable area of the anterior surface of the kidney. Only on rare occasions has the kidney been found completely surrounded by peritoneum and possessing a mesentery. The peritoneum can be moved over the anterior surface of the kidney for a short distance without affecting the position of the organ.

It is, I think, now generally recognized that the peritoneum does not hold in suspension the abdominal viscera. The viscera are retained in place chiefly by the abdominal and pelvic muscles. The folds of peritoneum maintain the organs in proper relation to each other, but do not support them. In prolapse of the kidney the organ descends behind the peritoneum, without drawing the peritoneum with it.

Gerota showed that if the peritoneum and adjacent organs be removed from the body the fixation of the kidney is not materially affected, all these attachments being merely accessory. The importance of the peritoneal relations to the kidney on the left side, from a developmental point of view, has already been described.

Certain ligaments which reinforce the peritoneum in the region of the kidneys have been described and may give some extra support to these organs. On the left side there is the phrenico-colic ligament, and on the right side the hepato-renal and duodeno-renal ligaments. The relations of the colon and the pancreas are all of importance in the fixation of the kidneys, whilst the renal surface of the spleen is closely fixed to the left kidney by the lineo-renal ligament and by a wide adhesion, which appears in the third month of development (Keith). This has to be considered in accounting for the rarity of mobility of the left kidney.

Summary of Factors which support the Kidneys.

The facts already arrived at show that the position of the kidneys in man is such that they are constantly exposed to the action of gravity, which tends to produce their prolapse. To prevent this descent taking place a number of factors give support to the kidneys; the most important of these appear to be the perirenal fascia and the maintenance of intra-abdominal tension. The perirenal fascia constitutes a well-defined sheath for the organs and has certain attachments to hold it in position, namely to the diaphragm, vertebral column, and musculature of the loin, whilst on the other hand it is intimately connected to the kidney.

In addition to this, the tone of the abdominal musculature plays an important part in retaining the kidney in its position in the loin. When, owing to laxity of the muscles, this upward thrust on the kidneys becomes lost, the fascial connexions will stretch and become lengthened and prolapse of the organ may occur. In males the shape of the renal fossa imposes an obstacle to the descent of the kidney, but in certain types of body-form, usually found in the female sex, the renal fossae are open and afford little support to the kidneys.

Such, then, appear to me to be the chief factors whereby the kidney is held in position in the loin.

8. Normal Mobility of the Kidney.

The kidney normally moves during respiration, and rises and falls with the action of the diaphragm. Earlier writers thought the kidney was a fixed organ, but Glénard in 1899 showed the organ moves with respiration. Kelly and Burnam state that the normal up and down movement during respiration varies from two to five centimetres; Thomson Walker observes the excursions vary from one-half to one and a half inches. The lower pole of the right kidney can often be felt in thin individuals during deep inspiration. It is easy to demonstrate in the dead body that the kidney moves behind the peritoneum, after opening the abdominal cavity. Rosenthal showed that in the female the kidney has a greater range of movement: this has been considered as due to the shape of the renal fossa in this sex. Also it can be shown that when the dead body is placed in the erect posture there is a slight descent of the organ. Hitzenberger and Reich have rendered the renal pelvis opaque to X-ray by injecting a solution of sodium iodide. On examining with the X-rays they find, on changing to the erect posture, the kidney sinks a distance of 10-20 mm.

On deep inspiration and expiration the renal pelvis rises or falls to the same extent as the diaphragm. In patients with enteroptosis the amount of displacement is increased and the degree of nephroptosis readily detected.

I have found on screen examination that in thin individuals, where it is possible to see the renal outline, the kidney descends one inch on deep inspiration. In one case, where a renal calculus was present in the kidney, radiograms again showed the organ moved one inch during deep respiration. The right

kidney moves more freely than the left with respiration (Billington). This is probably because the movements of the diaphragm are more directly transmitted to it through the liver, which descends into the renal pouch with each inspiration.

9. *The Aetiology of Movable Kidney.*

A movable kidney may be described as one which moves abnormally freely behind the peritoneum, whilst a floating kidney is one which rises or floats to the anterior abdominal wall. This latter type may possess a mesonephron and is then, of course, congenital.

Movable kidney is by no means a rare disease; it is, nevertheless, difficult to speak positively as regards its frequency. In the majority of cases it is the right kidney that is displaced, rarely both together, and rarest of all, as Fritz states, the left kidney alone. Morris says that the right kidney is twelve times more often affected than the left. Out of 245 cases Kelly and Burnam found the right organ alone mobile in 177 cases; Goelet in 85 cases found the right palpable in 84 patients, the left only once. The most important factor in the aetiology is sex, and since Rayer's time all agree that the condition is more common in women. The incidence in women as compared to men is given as 100 to 18 by Schultze, 100 to 12 by Glénard, 100 to 15 by Ebstein, and 100 to 1 by Dietl.

My own observations in hospital records show that Dietl's figures are nearer the truth, mobile kidney in males being very unusual. The condition is more commonly found in middle life, Morris stating that more than half the cases occur between 30 and 40 years.

The liability of women to renal displacements begins at puberty and increases with each decade to the fourth or fifth. As the female sexual characters develop the iliac crests expand outwards and the transverse intercrystal diameter of the body becomes greater than the transverse diameter of the lower part of the thorax. In children the pelvis is narrower than the chest. In this sexual character is one of the causes which render women more liable to kidney displacement than men.

Mobile kidney has been observed in young children, especially girls, from time to time by different writers. The fact that it has been seen at such an early age, and in some cases associated with ptosis of other organs, has been adduced as evidence in favour of the congenital nature of the condition. Stiller has reported several cases in infants, whilst Rosenthal observed 26 cases in young girls. Blum found 37 cases of mobile kidney in 106 children, 29 being in girls. It probably gives rise to few symptoms and so is not often recognized.

It is certain that movable kidney affects women more constantly than men, and that the right kidney is more often affected than the left. In 50 cases which I have looked up, operated for this condition at the Manchester Royal Infirmary, all were females, and in every case it was the right kidney which was treated.

In endeavouring to find a satisfactory explanation why mobile kidney is

more common in women than in men, and why the right kidney is more frequently affected, the following factors are of importance:

(a) *The renal fossae.* The kidneys lie in the renal fossae on either side of the spine. Being placed in a vertical direction their natural tendency is to prolapse when the body assumes the erect posture. The structures which lend support to the kidneys we have already considered, and now we have to discuss how the variations in outline of the fossae may affect the fixity of the organs. The kidneys are kept in position by the tone of the abdominal muscles: these muscles exert pressure on the viscera, which by their upward thrust support the kidneys from the front. Behind, these organs rest on the lumbar muscles, and their action is to press the kidneys forward, the combination of forces serving to support and maintain them in their correct position. Now, if the lumbar muscles become impaired and lose their tone, not only will the support they afford the kidney be lost, but, becoming lax and flabby, the size of the renal fossae will be increased and descent of the kidneys liable to take place.

An examination of the plaster casts of the renal fossae has shown certain differences in the two sexes (Figs. 1-8).

In the male the fossae are pear-shaped and become narrower at their lower end. Therefore, if the kidneys are kept pressed against the walls of the renal recesses, the very shape of the fossae tends to support the organs and prevent descent beyond a small degree.

Should abdominal tension be reduced by lack of tone of the musculature, the kidneys tend to come forward and this support from behind is lost. In the female the reverse is the case, the fossae are cylindrical in shape, or may widen out below, the female pelvis being relatively broader than the lower costal margin, and little or no support is afforded the kidneys from below. Should the tone of the musculature fall there is little hindrance to prolapse of the kidneys in the female sex. In one case that came under my notice, a female with freely movable kidneys, casts of the renal fossae showed they were cylindrical in outline and shallow in depth, and would afford little hindrance to the kidneys' descent. Body-form, or, in other words, the shape of the renal fossae, appears to have an important bearing on the predisposition to movable kidney: women with narrow chests and long slender bodies are liable to kidney prolapse.

The right renal fossa, though larger than the left, is deeper in the male, whilst in the female the two fossae are of approximately equal depth. In a comparison of the two sexes, the right fossa in the female is relatively shallower and so affords less support to the kidney in women.

The more frequent prolapse of the right kidney may also be explained on anatomical grounds. The right renal recess is roofed in by the liver, and this communicates to the kidney the downward movement of the diaphragm. Should the liver be enlarged or displaced so that this space is diminished, the right kidney in its turn will be forced down. On the left side the spleen, stomach, and colon occupy this region and increased pressure affects the kidney here to a much less degree.

(b) *Tight lacing.* The wearing of corsets among civilized women has been considered as one of the most potent factors in causing mobile kidney. Becker and Lennhoff examined 24 Samoan women and found mobile kidney in 6 cases. Zuckaki has found movable kidney in two-fifths of Egyptian women. These women had never worn corsets or constricting clothes, and the former race are noted for their athletic abilities. It is easy to observe that the 'low-waist line' is below the lower pole of the kidney, and corsets should rather tend to support the organ, except where pressure is exerted upon the upper part of the abdomen. I think it can be said that tight lacing alone is not capable of producing mobile kidney, and we know that mobile kidney appears in every class of life, whether corsets are worn or not.

(c) *Pregnancy.* Pregnancy has been considered by many authorities as accounting for the greater frequency of movable kidney among women than men. But statistics do not show this condition is more common among married women. McWilliam examined 61 cases of mobile kidney, and only 22 had borne children, whilst Kelly and Burnam found that out of 245 cases only 95 had borne children. I have frequently taken the opportunity to examine the kidneys in multiparae and have found them well fixed in position. Again, mobile kidney is found in nulliparae quite commonly.

It is, however, quite easy to observe that relaxation of the abdominal wall is present in women after multiple pregnancies, and after parturition the abdominal wall will be flaccid and toneless at first, and the pelvic diaphragm furnish a less efficient support for the abdominal contents. A weak and debilitated woman, assuming the erect posture too early after confinement, will be liable to suffer from a pendulous condition of the abdomen and prolapse of the viscera.

Prolapse of the kidney appears to be an anatomical defect, and the condition is perhaps aggravated by the changes that have been produced by pregnancy. The post-partum flaccidity of the abdominal wall and the loss of intra-abdominal tension tending to hasten the prolapse of the organs in one perhaps already predisposed to it by certain anatomical defects.

(d) *Tumours of the kidney.* Other causes have been put forward as bearing on the aetiology of movable kidney.

Riolan in 1682 thought that tumours and stones were the commonest cause of this condition. Such associations are unusual with mobile kidney and can only be the cause in rare cases. A tumour undoubtedly may cause enlargement of the kidney, and by increase in weight drag the organs downward. Volkoff and Delitsin dislocated the kidney by injecting mercury until its weight was doubled.

Hydronephrosis occurs not unfrequently with mobile kidney, but is usually secondary rather than primary. Bevers has recently described a case of hydronephrosis due to an abnormal renal artery, where the kidney was not found to be unduly mobile, and in a considerable number of cases of hydronephrosis I have seen the kidney appeared in its normal position.

(e) *Trauma.* Trauma, or severe muscular strain, precedes the discovery of

mobile kidney occasionally. Harris reports 41 cases where the condition was attributed to injury. It is difficult to see how trauma produces movable kidney in normal individuals; it may, however, draw attention to an abnormality already present. Cases following a sudden blow or injury are more like dislocations. In most reported cases the injury was inflicted years previously, before the symptoms developed. Arnim reports a case following a toss by a bull 21 years previously, Kispert following a fall 11 years earlier. On the whole, traumatism plays a small part in the production of mobile kidney, as is further shown by its rarity amongst men, who are more exposed to injury; though this immunity in men may perhaps be associated with their stronger abdominal muscles and the shape of the renal fossae. I only know of one definite case due to trauma, in a girl directly following a fall; nephropexy completely relieved her symptoms.

(f) *Loss of muscle tonus.* Weakness of the abdominal musculature and lowering of the intra-abdominal tension must be considered to favour the development of movable kidney. Intra-abdominal pressure is always positive under normal conditions, and assists in pressing the kidneys against the posterior abdominal wall and keeping them in place. Anything that relaxes the abdominal walls, such as the removal of large tumours or collections of ascitic fluid, may be said to favour the development of mobile kidney, likewise in women who have borne children frequently and numerously. These conditions further tend to dislocate the organs near the kidneys and stretch and strain the existing connexions which are present, and so conduce to prolapse of the kidneys. It has previously been pointed out that division of the muscles of the abdominal wall in the cadaver leads to descent of the kidneys when the body is placed in the erect posture. So perhaps in women of the poorer class, who have to get up and work too early after multiple pregnancies and the like, this factor may be of importance.

I have examined several cases where large ovarian cysts had been removed, and was unable to detect any abnormal mobility of the kidneys, and on inquiry cannot discover cases where excessive mobility has resulted after a proper and careful convalescence and where a good abdominal wall was present.

Extreme emaciation and loss of fat are regarded as a cause of mobility, on the supposition that the kidney is loosened in its fatty bed. It appears to me probable that those cases of nephroptosis which arise as a result of weakness of the abdominal musculature and loss of intra-abdominal pressure, are doubtless associated with some other factor. This seems to be the shape of the renal fossae, which in such cases appear to favour descent of the kidney, and a general weakness of the supporting structures. Nephroptosis may be part of a general disease which is manifested by prolapse of the liver, stomach, and transverse colon, a condition which is called splanchnoptosis. This connexion between ptosis of the kidney and abdominal viscera was first taught by Glénard. Glénard and Tuffier regard the condition as an organic defect, where, owing to laxity of their connexions and the abdominal walls, most or all of the viscera have dropped. It must be admitted that this view is not accepted by all; but it seems to apply to

a considerable number of cases. All varieties of type may be seen, from prolapse of one kidney to those in which all the abdominal organs have dropped.

A varying degree of neurasthenia accompanies mobile kidney in many cases. This may only become apparent when the patient discovers any abnormality is present. Such cases afford the least favourable prognosis for treatment. Suckling held that certain forms of insanity were due to nephroptosis and could be cured by fixation of the organ. It is impossible to say how far the symptoms find an organic basis in the kidney, and how far they are magnified by the neurotic element. It is difficult to say they will not continue as bad or become worse after operation. When descent of the kidney is associated with enteroptosis operation should not be undertaken. Examination of old hospital records show that some degree of visceroptosis was found in at least 50 per cent. of cases of movable kidney.

Recently, I have had the opportunity of examining seven women, all the subjects of displacement of the kidney.

Four had borne children, whilst three had not been pregnant. The body-form in all these women conformed to the long and slender type associated with 'open' renal fossae.

In every case I found there was a lack of tonus in the abdominal muscles, and there was evidence of prolapse of other abdominal organs.

Three cases had been submitted to operation for fixation of the right kidney, but they were still far from cured and showed signs of neurasthenia. One case has recently been operated upon for Dietl's crisis, it is too soon yet to foretell with what result. The remainder are being treated with belts and abdominal massage.

Displacement of the Right Kidney.

Displacement of the right kidney is far commoner than that of the left. Why is it the right kidney is more often prolapsed? The answer to this depends on several factors. The right kidney lies at a lower level than the left and descends further with each inspiratory movement of the diaphragm, due to the presence of the liver on this side. The effect of the liver, which occupies the subdiaphragmatic space, has already been mentioned in relation to prolapse of the kidney. Again, the fact that the right renal fossa is relatively shallower in the female, and perhaps larger than the left, is of importance, as has previously been shown.

In considering this fact the relationship of the colon and the kidneys must be taken into account. Each end of the transverse colon is fixed over the kidneys by the hepatic and splenic flexures. The hepatic flexure only comes into relation with a small area over the lower pole of the right kidney, whilst the splenic flexure and descending colon are closely related to the lower pole and outer border of the left kidney. Further, the fascial relations and peritoneum covering the anterior surface of the left kidney are reinforced by a triple layer of peritoneum, as already described, during the course of development, and so give increased security to the organ on the left side.

Traction of an overweighted caecum and colon, the hepatic flexure being more liable to faecal accumulation, drags on the kidney, and by inducing mobility may affect the fixed position of the organ.

Lane regards chronic constipation as an important factor in the production of mobile kidney. He describes numerous bands and adhesions passing between the caecum, ascending colon, and right kidney, which by traction produce prolapse of the organ.

The right kidney is exposed to push from above through the liver and pull from below through the overweighted colon, all of which tend to increase its liability to prolapse.

The increased length of the right renal artery, being 2 cm. longer than the left, is also considered a reason of its less secure fixation.

The left kidney has certain additional means of support. The relation of the colon and its fascial connexions have already been mentioned. The left kidney is bound to the spleen by the lienorenal ligament, and the spleen is attached by its suspensory ligament to the diaphragm. Also the pancreas has important relations to the left kidney and the renal vessels, and gives further fixation. The left suprarenal vein joins the left renal vein and acts as an additional mainstay, since the suprarenal does not follow the kidney when prolapse occurs, being firmly fixed in position. Further, the contents of the left hypochondrium have little tendency to displace the kidney as compared to the liver on the right side.

10. *Summary of Factors relating to the Aetiology of Displacement of the Kidney.*

1. The adoption of the erect posture by man has resulted in a natural predisposition to prolapse of the kidney.

2. The predisposing cause of mobility of the kidney depends on certain types of body-form as shown by the shape of the fossae in which the kidneys lie.

3. Mobile kidney occurs more frequently among females, owing to the fact that the renal fossae are open or wider below than above. In males they are pear-shaped and narrower below.

4. The determining factor in many cases is a relaxed abdominal wall, and this affects females more than males, due to the inferior muscular development in women, pregnancy, and the different mode of living in the two sexes leading to loss of muscle tonus in the female.

5. Displacement of the right kidney is more common, due to the shape of the renal fossa, and the presence of the liver on this side. The left kidney is more securely supported by neighbouring structures.

6. The liability of women to renal displacement begins at puberty, as after this period certain changes in the pelvis occur, rendering them predisposed to prolapse of the kidney.

Conclusions.

1. The kidney, suprarenal body, and perirenal fat are completely enclosed in a single fascial sheath—the perirenal fascia.
2. The perirenal fascia has firm attachments to the diaphragm, vertebrae, and transversalis fascia.
3. The kidneys are mainly held in position by the perirenal fascia, the renal pedicle, and the maintenance of intra-abdominal tension.
4. The shape of the renal fossae is of importance in connexion with prolapse of the kidney.
5. The fact that prolapse of the kidney is commoner in females and on the right side can be explained on anatomical grounds.
6. The perirenal fat is always present at birth.

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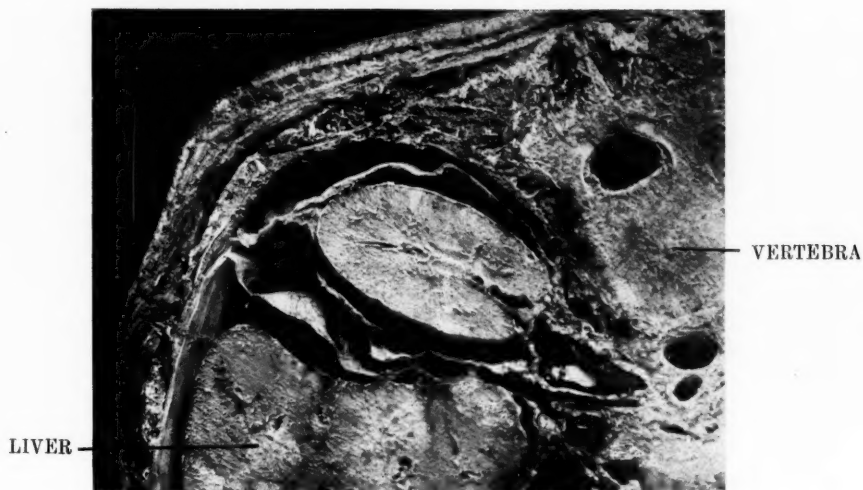


FIG. a

Transverse section through right kidney of an adult male at level of hilum. Peritoneum separated in front and anterior and posterior layers of perirenal fascia are seen freed. The two layers unite at outer pole, and after enclosing some fat pass as band to join transversalis fascia behind peritoneum. At inner pole the fascia is attached to vertebra and over great vessels as described in text.

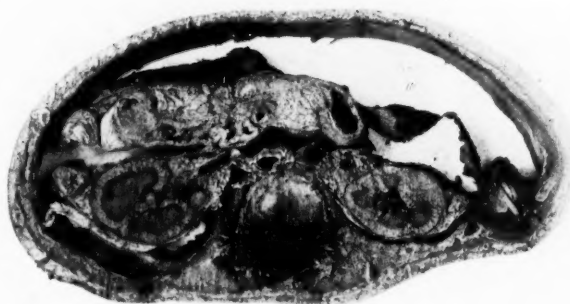
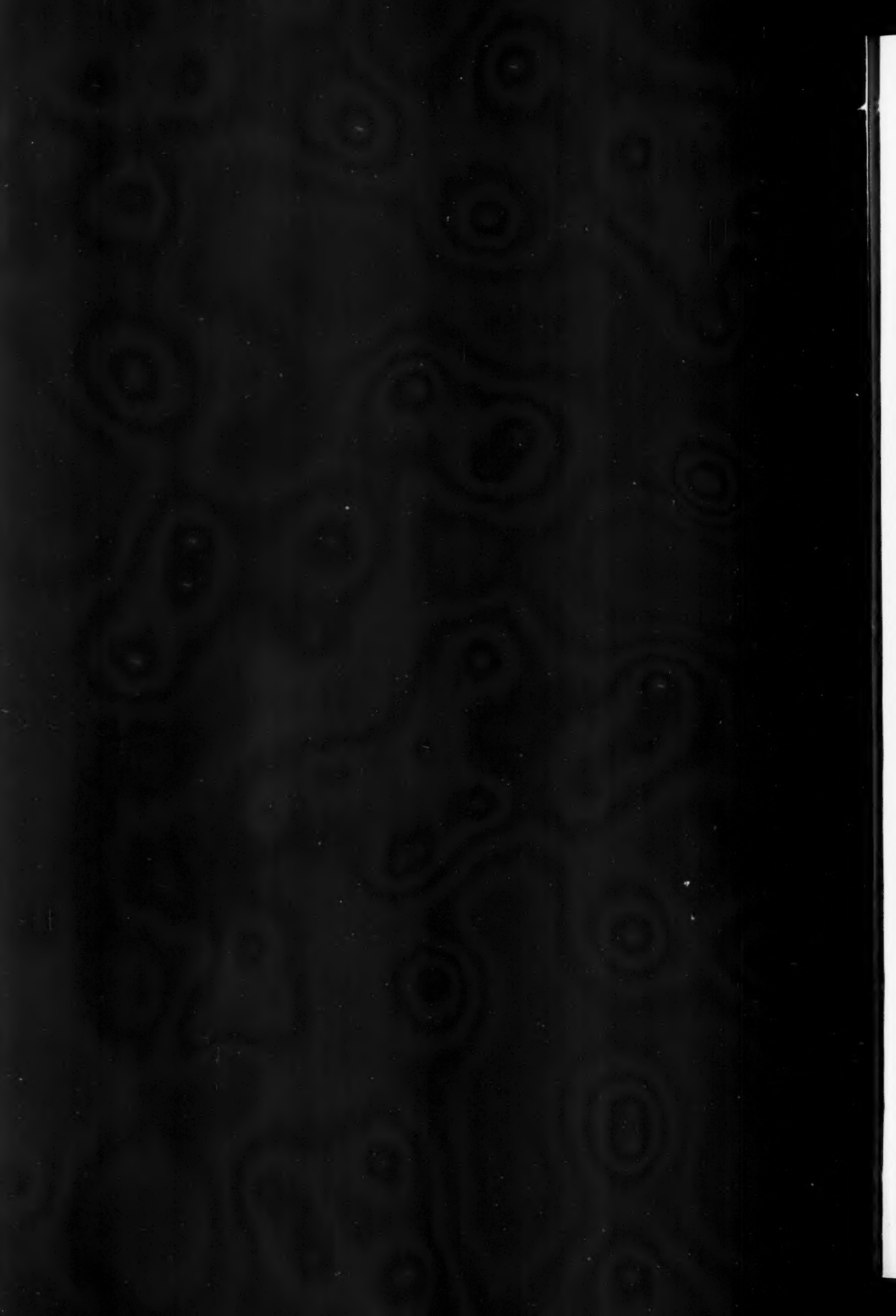


FIG. b

Transverse section through body of full-term foetus. The deposit of fat at the inner and outer poles of the kidney is shown. On the right side the peritoneum is drawn forwards. The two layers of the perirenal fascia are seen uniting at outer border of kidney and as a band pass to join transversalis fascia. At the inner border posterior layer is attached to spine, whilst anterior layer ends over great vessels and behind pancreas. On left side association of colon and kidney is shown.



DIAPHRAGM



SIGMOID

Vertical section through left kidney of an adult.

The diaphragm is shown above, the stomach and pancreas in front of the kidney.

Below, the sigmoid and peritoneum are reflected to the right. The layers of the perirenal fascia are separated from surrounding structures and clearly demonstrated. Below, they do not fuse and a potential channel is formed. Above, they unite and join the diaphragm.

The peritoneum and fascia over lumbar muscles are seen as distinct layers. All fat has been removed.

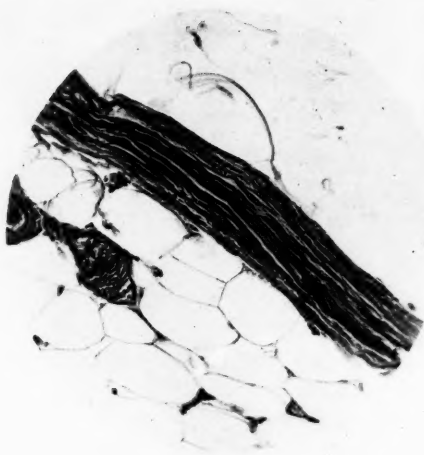


FIG. a

Microphotograph to show the structure of the perirenal fascia.

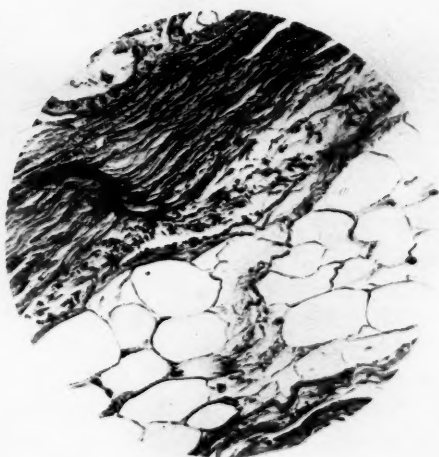


FIG. b

Microphotograph to show one of the fine connective tissue strands passing from the kidney capsule to the perirenal fascia through the perirenal fat. Two renal tubules are seen at the top of the photograph.

ENDOCARDITIS LENTA (CHRONIC ULCERATIVE ENDOCARDITIS)

A NOTE ON THIRTY CASES SEEN IN CIVIL PRACTICE SINCE THE WAR

By CAREY F. COOMBS

With Plate 11

THAT an ulcerative infection of the cardiac valves may run a long course before its fatal issue is accomplished is no new fact. In one of the earliest numbers of this *Journal* it was noted by the late Sir William Osler (1); also by Sir Thomas Horder (2); and, at approximately the same time, by Libman (3) in New York, and Schottmüller (4) in Hamburg. Of the various titles affixed by these writers to the disease which they describe, that of 'endocarditis lenta' has been preferred to the others, partly because it does not pretend to anything more than a clinical definition of the type of case under consideration. Obviously, a title based on a knowledge of the aetiology of the disease is much to be preferred; but so far that knowledge is not adequate, and it is because some of the features of the cases below appear to afford a clue to their aetiology that this note has been written.

In the first place, it is well to state as clearly as possible what is included under the term 'endocarditis'. Stress must be laid on the distinction between endocarditis and carditis. In a recent paper (5) the writer showed that whereas in rheumatic carditis there is endocarditis which arises simultaneously with similar and equally extensive lesions in other parts of the heart, particularly the myocardium, there is in this group of cases about to be studied an endocardial lesion which is predominant over any other morbid changes that may be found in the same heart, not only because it is far more extensive than those other changes, but also because everything goes to show that it is the source from which they arise by embolism or by direct extension. The first is a carditis, a simultaneous attack on the whole heart, of which the endocardial inflammation is one of several results; the other is an endocarditis, a direct invasion of the inner lining of the heart, and at first, at any rate, of that part of the heart alone. Similarly, the endocardial lesions of syphilis, that other great provocative of endocarditis, must be regarded as one feature only of a generalized invasion of the heart as a whole, a progressive carditis. If, then, we take away from the general mass of cardiac infections these two particular groups, the carditis of rheumatism and

that of syphilis, what remains? A congeries of cases in which micro-organisms of all kinds have succeeded in gaining hold of some single part of the cardiac structure; sometimes of the pericardium alone, sometimes of the endocardium, very occasionally of the cardiac muscle. The title 'endocarditis' is a convenient label for cases in which the infection is limited, at all events in its onset, to the endocardium. If a logical subdivision of this group should be attempted, it would be into aetiological sub-groups. Many would argue that such a subdivision is already possible, and they would be satisfied with labelling their sub-groups 'pneumococcal', 'streptococcal', and so forth; forgetting that in the causation of disease the soil may be more important than the seed. But if no such aetiological classification be attempted, the only alternatives are, first, that which proposes a definition of classes according to their prevailing anatomical features, such as 'aortic', 'mitral', and so on; and second, that which would define these infections in terms of their effects on the work of the body. Unfortunately, taking this latter line, we can get little farther than to classify the infections of the endocardium according to the facility with which they bring life to an end; and since it is convenient to recognize three grades of comparison in most of the facts of human experience, here also 'endocarditis' may be classified into groups, including those cases where, on the one hand, the infection kills the victim easily, those where, on the other hand, it barely succeeds in doing so, and those which lie somewhere between. Such a classification has one obvious drawback; it is difficult to place certain 'borderland' cases in one or the other group. But, as a matter of experience, this plan of subdivision works better than one might expect. At one end of the scale come those cases, seldom recognized during life, in which some chronic illness is terminated by endocardial infection which meets with but little resistance. At the other end is the case of 'endocarditis lenta' running a course of months or years, with little or no fever, and displaying after death every anatomical sign of a stubborn opposition to the infection. Between these extremes lies a group of cases exhibiting what is still regarded as the characteristic picture of ulcerative endocarditis: a course of several but not many months, oscillating but continued fever, and, *post mortem*, a suppurative reaction of the endocardial tissues to the microbic attack. In separating the thirty cases to be discussed below from this group there was but little difficulty; four cases have been transferred to this middle group which might have been included by some under the heading of endocarditis lenta, on the ground that the course was too short and the fever too pronounced.

The distinction between the group now to be discussed and those others which most nearly resemble them can hardly be written down more clearly, and perhaps a better plan of defining them will be to proceed to give a short description of their principal features, turning later to a detailed description of those aspects of the disease which are particularly under review in this article.

Aetiology.

The most striking feature of this group has been the extraordinary predominance of males, who represent twenty-nine of the total, the only other one being a girl of 15. The ages of the twenty-nine men range from 20 to 44, the average being 30.6. Of these twenty-nine men, the majority, namely twenty-two in all, had served in the Army during the recent war, all of these except one having been overseas. A more detailed analysis of their military service will be made when the question of aetiology is more fully discussed later. Of the whole group of thirty patients, eleven only gave a history of rheumatic fever, or other forms of rheumatic infection. It is interesting to note that, of the eight men who had no military service, seven gave a history of previous rheumatism, the cardiac lesions which resulted having been responsible for their failure to pass into the Army. Of those who had seen overseas service only four showed any rheumatic history. A positive Wassermann reaction was found in three cases only, and, though it was not sought for in every case, there was reason to think that, had it been so, no great number of unsuspected cases of syphilitic infection would have been brought to light.

*Morbid Anatomy.*¹

It will hardly be necessary to enter upon a detailed description of the anatomical changes seen in thirteen of these cases, but certain points which appear to be characteristic of the group may, perhaps, be brought into special prominence.

First, the remarkable consistency with which the aortic rather than the mitral valve was attacked. This was the case in eleven of the thirteen autopsies. Of these thirteen, four were men who had not been in the Army; of these four, curiously enough, two showed predominant mitral lesions.

Second, the smouldering character of the infection. To find the micro-organisms at all is very difficult. Blood cultures made during life are consistently sterile. Even the vegetations themselves are not very productive. Not only do sections display micro-organisms in small and thinly scattered groups contrasting remarkably with the masses to be seen in the acuter grades of endocardial infection; but actually it may be difficult to cultivate them on artificial media. We have not made systematic inquiries into the character of the organisms, but such as have been found by Dr. Geoffrey Hadfield, Pathologist to the Bristol General Hospital, have been non-haemolytic streptococci like those growing normally in the mouth and gut of man. Such an infection excites only a quiet resistance. The valves themselves are often much sclerosed and deformed, and impregnated with lime, facts which attest the long and even character of the struggle. Underneath the infected surface there is little or no polymorphonuclear congregation, but a deep zone of formative reaction fading off gradually into areas of fibrin with

¹ The investigations briefly summarized here were carried out with the help of a grant from the Medical Research Council.

calcification. The reaction to infarcts, both in the heart and elsewhere, seldom amounts to more than a quiet proliferation of the fixed cells of the part—a reaction such as one might expect round any foreign body suddenly projected into a normal organ. The renal changes described as characteristic of chronic ulcerative endocarditis, by Baehr (6) and Gaskell (7), were found in most of these cases. Their most striking feature is the gradual silting up of the capillary tufts of the glomeruli by fibrin, presumably derived by embolism from the inflamed valves. The glomeruli, as such, disappear, being converted into homogeneous balls of deeply-staining material; and the tubule arising in a glomerulus which has thus been ruined undergoes atrophy. But all this excites no great inflammatory reaction, beyond aggregation of lymphocytes just under the capsule of the kidney. The inference is that the emboli carry little or no microbial irritant. The huge, loosely branching scars seen all over the ventricular wall in these hearts show in all their stages of development a quiet formative reaction, also proof of the absence of any strongly irritative organism from the emboli to which they owe their initiation.

Third, in most cases there is no evidence of previous cardiac infection. The mitral valve is intact, except when it has become the seat of the lethal infection.

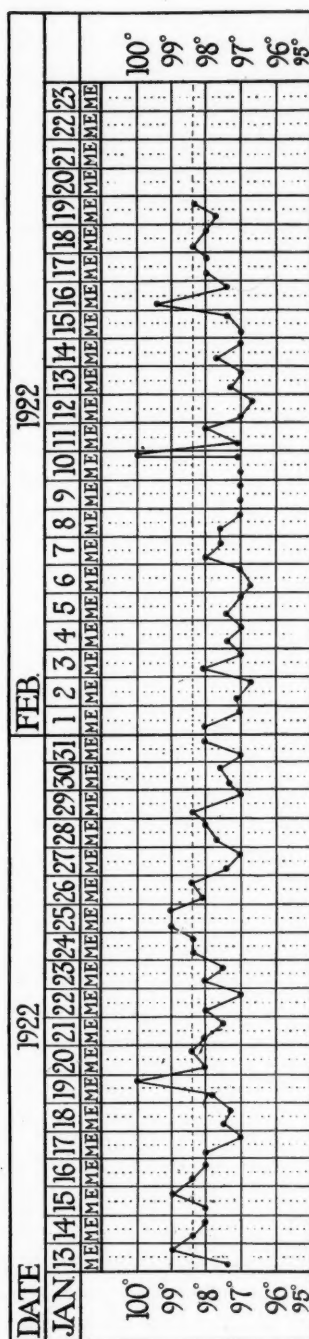
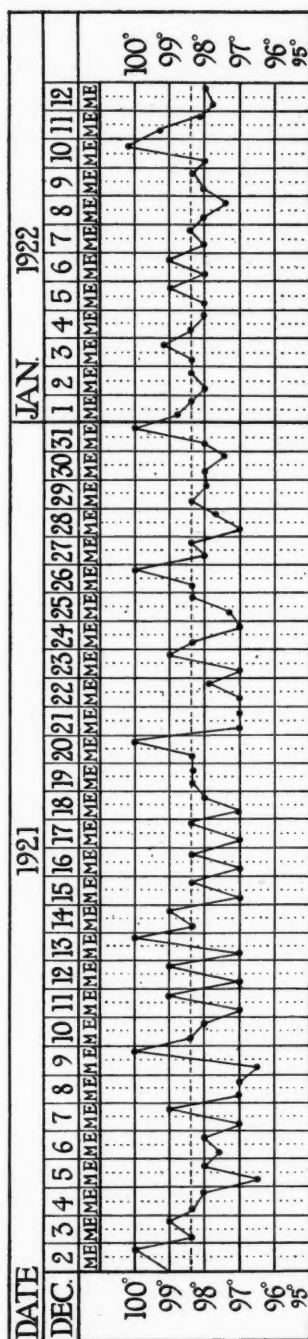
Fourth, the masses of fibrin attached to the valves grow to a remarkable length, out of all proportion to the smallness of the area of endocardial inflammation from which they spring. It is not easy to see what the explanation of this can be, and perhaps it should scarcely be singled out as a feature of this particular group of cases of endocarditis (Plate 11).

Morbid Physiology.

In persons with chronic valvular disease the chief source of disability is mechanical interference with function; in streptococcal infections, the action of the bacterial toxins on the vital functions generally. These two factors are so intimately blended in the cases under consideration that it is difficult to say which has been the more powerful instrument of downfall. Perhaps one might say that in the earlier stages toxæmia, in the later mechanical inefficiency, appears as the predominant partner. To these must be added a third, embolism; dramatically obvious when it is a single gross infarction of the brain that kills, but no less deadly when it takes the shape of steadily progressive destruction of renal glomeruli.

Symptoms and Diagnosis.

The first and most striking feature of the clinical course of these cases is their insidious origin. There is a gradual loss of flesh and strength, followed by pallor and dyspnoea, increasing so slowly as to attract little attention until some one who sees the patient for the first time or after a long interval is alarmed at his appearance. The patient himself seems to be lulled by a false sense of well-being into a state of complacency which contrasts most sharply with his appearance. Moreover, the men selected by this disease for attack are of the kind



A temperature chart from the patient whose case is described under Plate 11.

that does not like to confess to ill health or to send for the doctor; men of the industrious sort who are apt to despise sickness and to regard themselves as beyond its reach. This gradual decline of strength has been the outstanding feature of a majority of the cases—in all, indeed, but seven. These latter were patients whose hearts had for some time been known to be diseased; to the long-standing physical signs had been added symptoms arousing suspicion, confirmed by the subsequent course, and in five instances by autopsy, of the addition of slow, but active, infection to the old valvular lesion. But the other twenty-three patients have come under observation by reason of general ill health, and the presence of cardiac disease has been discovered as a new fact. The discovery has not always been made at once; one man, seriously ill and under careful observation for several months before death, developed no definite physical signs of aortic incompetence till a week before death. Another man was admitted from my out-patient department under a diagnosis of endocarditis lenta, because he had lost weight and showed a violaceous cyanosis, clubbing of the fingers, and enlargement of the spleen. There were no physical signs of cardiac disease. He refused to stay in hospital because he did not feel ill enough. When seen nearly a year later (under the Ministry of Pensions) he had developed pronounced aortic incompetence, and an autopsy proved that this was due to progressive endocarditis of the kind now being described. In a majority, then, the dominant clinical fact has been progressive debility; in a minority, signs of cardiac disease. In all cases, however, some evidence of cardiac disease was found at length, and in 80 per cent. the predominant physical signs were those of aortic regurgitation. In addition to the pallor, dyspnoea, and loss of flesh and strength already referred to, results of toxæmia were to be discovered in splenic enlargement, once or twice reaching an extraordinary development, noted in 52 per cent.; and in slight and occasional rises of temperature (see chart) in 61 per cent. Finally, the diagnosis is confirmed by discovery of embolic phenomena. In only five cases did gross embolism—of brain or limb—occur; but petechiae were found in 50 per cent., while in another case 'Osler's nodes' developed in the fingers and the palm of the hand, and in yet another there was a free eruption of hæmorrhagic bullae over the face and arms. Blood was found in the urine in 54 per cent. of the cases, often only after repeated search with the microscope; albumin being present in 65 per cent. Hæmorrhages into the retina are recorded as present in only three of the nineteen cases in which a note as to the condition of the fundi was made.

The course of the disease is slow. One of my patients first noticed dyspnoea in December 1918, before demobilization. This got worse so slowly as to attract little attention until January 1921. By this time he was already very anaemic. In July 1921 he began to show obvious signs of cardiac disease, but he lived on till the spring of 1922, nearly three years and a half after the beginning of symptoms. One man died suddenly of cerebral embolism, and three of cardiac failure which had not been foreshadowed by any change in symptoms or signs.

Treatment.

Unhappily, treatment has proved ineffectual. It might have been thought that a disease in which the balance between the invader and invaded appears to be so nicely adjusted would prove amenable to means for the overcoming of the infection. The intravenous injection of various antiseptics, the administration of antistreptococcal sera, and the use of autogenous vaccines, have all failed to do good. It is possible that treatment by rest in the open air might prove as effective as it has in pulmonary tuberculosis. It is certain, however, that just as early diagnosis is essential to success in the treatment of pulmonary tuberculosis, so also it would be in endocarditis lenta; and this is one of the great obstacles to an effective therapeutic plan, for, by the time the patient comes under observation, the disease is often advanced and obviously beyond the reach of cure. It seems as if in this disease, as in so many, indeed in all other infections, the hope of the future must lie in a plan of prevention founded on a more accurate knowledge of aetiology; and it is to this end that the notes which follow have been written.

Further Considerations as to Aetiology.

When we turn back to look at the conditions under which this kind of cardiac infection was allowed to occur, the attention is at once arrested by the remarkable fact that twenty-nine of the thirty patients were males. Prior to the war the sex incidence of the disease was approximately equal in the experience of a number of observers. The largest total of cases available is Dr. Libman's. He has kindly furnished me with data collected in 1917 to the effect that of 157 patients 99 were males and 58 females. The European figures are more nearly even in their division.

Another remarkable feature of the post-war type of endocarditis lenta is its relative independence of pre-existing valvular lesions. In every one of the six cases already alluded to, as seen prior to the war, there was a history of rheumatic infection preceding by some years the final cardiac infection; in several of them a chronic rheumatic lesion of the mitral valve was observed to exist for several years before the onset of the symptoms of active infection which passed slowly from their inauguration to a fatal issue. A similar experience was recorded by the writers referred to above; each of them states that evidence of previous rheumatic infection was forthcoming in a majority of these cases. Indeed, it is not too much to say that the general conception of chronic ulcerative endocarditis, formed on the basis of pre-war experience, is that of an insidious re-infection of the residual valvular lesions of rheumatic heart disease, difficult to detect during life, unless it is looked for systematically. Now, in the post-war cases of endocarditis lenta, a history of previous rheumatism is relatively rare, as Starling (8) was the first to show. Among these thirty patients such a history was obtained in only ten. Of the twenty-one ex-service men a history of rheumatic infection could be obtained in only four; and though

evidence of syphilitic infection was obtained in three more, neither this nor rheumatism could be held accountable for a majority of cases.

A third point of contrast is to be noted in the incidence of the disease on a particular valve. Whereas five out of the six pre-war cases exhibited lesions of the mitral rather than the aortic valve, and about two-thirds of the cases recorded by the four writers alluded to, the predominant lesion was aortic in 53 per cent. of the post-war cases examined anatomically; in 80 per cent. of all cases if physical signs be accepted as evidence.

Of all these three divergences of the post-war cases of endocarditis lenta from the picture of the disease as it was familiar before the war, the most striking is the remarkable sex-incidence. It is probable that my experience in an average period of three years and a half should include more than one case in girls and young women, but in these particular years it has not, though cases have been looked for carefully. Many patients with valvular lesions of old standing have been suspected of active infection, and have been kept under close observation. A small number of acute cases has been seen during the same time—young women with post-rheumatic lesions of the mitral valve developing high and continued fever with embolic symptoms, running a course not exceeding three months; but only one of the slow febrile kind. On the other hand, there have been in the same period twenty-nine cases in young men; and this list might have been increased by the addition of seven others, but that the severity of the symptoms, the height of the fever, and the shortness of the course have appeared to place them in the 'acute' group. So that, even if a rather more acute grade of infection should be included under the title of endocarditis lenta, the male patients would still constitute at least four-fifths of the whole group. This is so striking a departure from the usual sex-incidence as to demand closer scrutiny. In the first place, more than half the male patients were between twenty and thirty years of age. Secondly, twenty-two of the twenty-nine men had served in the Army in the recent war. Thirdly, among these twenty-two men the other two points of difference from the pre-war type of endocarditis lenta were much more pronounced than in the men who had not served in the Army. The following table shows that clearly:

	Total.	Previous Rheumatism.	Evidence of Syphilitic Infection.	Percentage with no previous Infection of the Heart.	Percentage with Aortic Lesions predominant.
Men with no military service	7	6	0	14.2	57
Men with home service only	1	0	1	0	100
Men with overseas service	21	4	2	71.4	100

The inference to be drawn from this is that the change in the type of person subject to endocarditis lenta has been due to the development of the disease in men who served in the Army during the war. The objection may be raised that if this be so it should be possible to demonstrate an increase in the total incidence

of the disease. But any statistics of the incidence of endocarditis lenta in relation to the whole population would be based on such uncertain data as to be unreliable. In my own experience the number of cases of endocarditis lenta examined *post mortem* at the Bristol General Hospital between the end of 1918 and July 1922 was eleven, while during the period 1908 to 1914 there were only six. But such totals are too small to be useful, and any attempt to collect figures on a larger scale—for example, from the whole of England—is beset with invincible difficulties. The experience of other British observers appears to vary considerably. Starling (8), Cotton (9), and others have seen a number of cases among ex-service men. In this connexion it is interesting to note that in Cotton's Ministry of Pensions Clinic about 8 per cent. of his men with valvular disease of the heart showed definite signs of active endocardial infection, a figure which agrees closely with that of my colleague Dr. C. E. K. Herapath, who is in charge of the Bristol Clinic. The data with which he has kindly furnished me show that of a total of one hundred and eighty-eight men with valvular disease under his care at the clinic, thirty-seven were possibly, and thirteen, or 7.4 per cent. of the total, were probably, suffering from a slow progressive endocarditis.

There are, however, other British clinicians whose experience lends no support to a belief in the prevalence of endocarditis lenta among ex-service men. Possibly those discrepancies may in part be explained by difference in the rate of recruiting, and other similar differences in the conditions of living during the war years. However this may be, the fact that there is a relation between endocarditis lenta and service in the Army in the population of the Bristol district appears beyond dispute. It remains to see, if possible, what is the nature of that relation. To that end I have analysed the notes of 33 cases in ex-service men, most of whom were referred to me by the Ministry of Pensions. In parenthesis it may be noted that these cases appear to be much less frequently encountered than they were a year or two ago. The results of the analysis, so far as they are susceptible of statistical expression, are summarized in the following table:

Total cases	33
Infected before enlistment—rheumatism, 4; syphilis, 2	6
Service record. Average duration in years	3.05
Served in France only	22
" " East only	5
" " France and East	1
" " France and Italy	2
" " Home only	1
Doubtful (possibly France)	2
Infantry or artillery service	80 %
Lesions during service:	
A. General (P.U.O., trench fever, malaria)	16
B. Local. (1) Respiratory (influenza, gassing, &c.)	9
(2) Alimentary (dental, sepsis, colitis, &c.)	4
(3) Cutaneous (gunshot wounds, boils, &c.)	8

It is clear from this summary that, as one would expect, the predisposition of the ex-soldier to endocarditis lenta is not due to infections of the heart prior

to enlistment, since approximately four-fifths of the cases, even after the Ministry of Pensions had scrutinized their histories, failed to disclose any evidence of such infections. On the other hand, there is a close relation between service in France and the contraction of this disease; but, unless the percentage of men serving overseas whose service lay partly or wholly in France is used as a basis for such figures, too much stress must not be laid on this. The facts as to lesions and diseases contracted during service are of course open to the criticism that it is quite impossible to assess in figures the liability to injury of the various 'portals of entry' of infection; but it does seem reasonable to conclude that the reason why soldiers become victims of endocardial infection does not lie in their liability to be invaded by micro-organisms through any particular tract. It cannot be denied, of course, that the soldier was exposed to unnatural risks of infection through his alimentary and respiratory mucous membranes as well as through his skin; but no one of these surfaces seems to have been pre-eminently guilty of admitting the micro-organisms by which the heart became infected. Neither can much be made of the figures indicative of lowering of resistance by general infections. The incidence of these among the men under consideration was, probably, not higher than the average incidence of such sickness among the British armies in the field.

There is, however, a very remarkable fact, only imperfectly presented in the table by the statements that 80 per cent. of the men were engaged in the more strenuous forms of military service and that the average duration of service was 3.05 years, or nearly three-quarters of the whole length of the war. That fact is one which is not susceptible of arithmetical statement. It is this, that almost without exception the men whose military service was followed by the development of endocarditis *lenta* were men of fine physique and morale: men who joined the army early, served with all their might, and exerted themselves to the utmost limit of their physical powers. The only striking exception to this rule was that of the man who had only served at home. He was a small and stunted man with chronic otorrhoea and unmistakable evidences of tertiary syphilis. This man excepted, the uniformity with which the men have been characterized by good physique and keenness of spirit is such as to imply some causal relationship. Looked at from the obverse side, the same fact is equally striking. At the bases and elsewhere, both at home and overseas, there were large numbers of men of indifferent physique serving in the Army; yet I have not so far encountered a single example of chronic endocardial infection among such men.

So constant has this relation between physical fitness and strenuous exertion on the one hand, and proneness to endocardial infection on the other, proved itself to be, in the experience of others as well as of myself, that a belief in a causal relation between the two can hardly be avoided. The action of excessive fatigue in predisposing the body to infection is of course a familiar fact, though it does not often, perhaps, stand forth as the predominant factor. That there may be a biochemical link between fatigue and infection is suggested by some of Walker Hall's (10) work on the effect of dilute acids on the growth of bacteria in

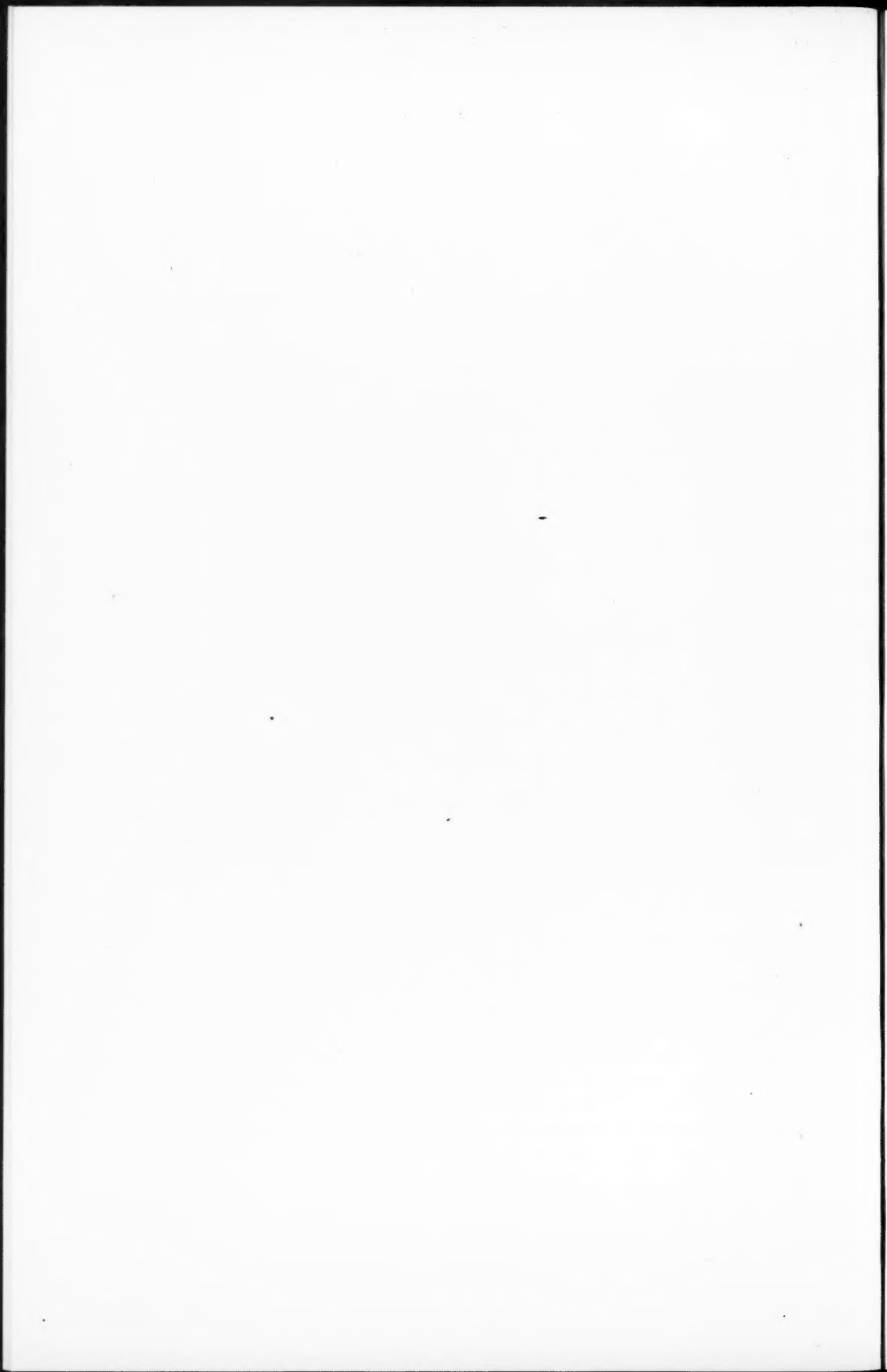
blood cultures, in which it was shown that 'blood cultures may be accelerated by the addition of 1/200 normal solutions of lactic or nitric acids to adequately buffered nutrient broths'. It is possible that the prolonged and excessive muscular efforts made by men in the stress of modern military service may raise the lactic acid content of the blood enough to make all the difference to an invading micro-organism of low virulence—enough to make growth to the point of pathogenicity possible where otherwise it would fail to reach that level.

Summary.

The group of 30 cases of endocarditis lenta, seen in civil practice since the war, is chiefly remarkable because 29 of the 30 cases occurred in men between 20 and 44; of whom 22 had served in the Army during the war. Reasons are given for believing that the most constant causal factor was excessive fatigue.

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The aortic and mitral valves of a patient whose chart is shown in the text, an ex-service man, aged 25, whose illness lasted about two years. The lesions, which are extensive, are limited to the aortic valves. There is no evidence of recent or of previous endocarditis of the mitral valve.

A CLINICAL INVESTIGATION INTO THE RELATIONSHIP OF THE FAT-SOLUBLE 'A' VITAMIN TO THE AETIO- LOGY OF RICKETS

By DOUGLAS GALBRAITH

(From the Medical Department of the Royal Hospital for Sick Children,
Glasgow)

With Plates 12-14

THE great amount of experimental work which has been done during recent years, and the assumption that animal rickets so induced is identical with that developing spontaneously in children, have led to far-reaching conclusions regarding the cause of rickets. On the ground of much of this work it has been concluded that, of all the predisposing causes, errors in diet are the most important, and, of these, a deficiency of the fat-soluble A vitamin has received most credence. Eventually, however, one must come back to the child as the final court of appeal, and it was to put the fat-soluble A deficiency theory to the clinical test that the following research was undertaken.

If deficiency of the fat-soluble A vitamin is the principal aetiological factor in rickets then we should expect:

- (1) that no child observed on a diet containing a sufficiency of the vitamin should develop rickets;
- (2) conversely, that children on a diet not containing a sufficiency of the vitamin alone should develop rickets;
- (3) that a deficiency of this vitamin in the diet should be apparent in the previous dietary of definitely rachitic children, and
- (4) that healing should not occur unless a sufficiency of the vitamin be presented.

In view of the above considerations the general plan of the investigation was as follows:

- A. The observation for long periods of children on a definitely *fat-sufficient* diet.
- B. The observation for long periods of children on a definitely *fat-deficient* diet.

C. The investigation of the diet histories from birth of definitely rachitic children and the estimation of the probable fat content of these diets.

D. The observing of the effect of various remedial measures in children both on fat-sufficient and fat-deficient diets.

Criteria of Diagnosis.

It is of prime importance in an investigation of this nature to state the grounds on which an opinion as to the presence or absence of the disease was based. Although, naturally, attention was paid to the clinical manifestations, a diagnosis of rickets was never made unless confirmed by a positive radiographic picture. These radiographic changes are so well known and have so recently been described by Park and Howland (1) that no detailed description need be given here. The wrist was the part selected for radiograph. In my experience the earliest change noted was a widening of the lower end of the ulna: this change may precede the typical irregularity of the ends of the bones even by so long as two months. Delay in the appearance of the centres of ossification of the carpus was not given prominence as a diagnostic point because other conditions, such as gastro-intestinal troubles and malnutrition, influence the time of appearance of these centres. The usual *clinical signs*—delayed closing of the fontanelles, craniotabes, delayed or irregular dentition, epiphyseal enlargement, beading of the ribs, and curvature of the long bones—were observed. I believe that a slight enlargement of the epiphyses at the wrist is the earliest and most constant sign; whilst, on the other hand, the 'rickety rosary', both as a positive and negative sign, is, in my experience, unreliable in the diagnosis of early rickets. *Symptoms of rickets* are generally considered to be invariably present, but I have found that in uncomplicated cases of the disease they were often entirely absent. Frequently I have observed children continue to be plump, of good colour, and to increase steadily in weight while successive radiographs showed progressing rickets. Head-sweating, tenderness of the limbs, gastro-intestinal disturbances, and failure to thrive were often conspicuous by their absence.

The Standard of Fat Intake.

Before one can decide that any particular diet is fat-sufficient or not it is essential to have a knowledge of the normal fat requirements of the healthy infant. The ideal, I think, may be taken as that contained in the amount of human milk consumed at any particular age. Accordingly I have estimated the amount of human milk required at each month up to one year to supply the caloric needs of the infant (Rubner's scale). For example, at six months 570 calories are required: estimating the caloric value of breast milk at 20 per ounce, and its fat content at 3.25 per cent., 28.5 oz. of breast milk, containing 27.8 grm. of fat or 3.9 grm. per kilo, would be the ideal fat intake at this age. The fat

percentage of human milk, as given by different investigators, varies considerably, but 3.25 per cent. seems a reasonable average. It should be stated that *in all cases the children were fed according to age, i. e. according to the expected weight and not the actual weight.* The following table shows the estimations of the ideal fat intake for the various months during the first year of life:

TABLE I. *Calories required—Amount of Breast Milk and Ideal Fat Intake for Different Months during First Year.*

Month of Life.	Calories required.	Amount of Breast Milk necessary.	Grm. of Fat (Ideal Fat Intake).
		oz.	
1st	370	18.5	18.0
2nd	430	21.5	21.0
3rd	470	23.5	23.0
4th	510	25.5	25.0
5th	540	27.0	26.3
6th	570	28.5	27.8
7th	590	29.5	28.0
8th	610	30.5	29.7
9th	620	31.0	30.25
10th	630	31.5	30.7
11th	650	32.5	31.6
12th	670	33.5	32.5

The majority of children were fed on an artificial diet, and cow's milk was the one most commonly used. A 3 per cent. fat standard for cow's milk has been assumed throughout, on account of the following facts kindly supplied to me by the Medical Officer of Health for Glasgow. Of the official samples of sweet milk examined during the year from July 1921 to August 1922, the average monthly fat percentage amounted to 3.4, the lowest monthly average being 3.38, and the highest 3.62. The average for the six winter months was slightly higher than that for the six summer months, being 3.48 per cent. in the former and 3.46 per cent. in the latter. A fat percentage of 2.85 or less was usually taken as the index for prosecution, and of 824 official samples examined 97.2 per cent. contained a legal sufficiency of fat. It seemed possible, however, that the milk sold in the better class districts might contain a higher percentage of fat than that sold in the poor class districts, thus raising the city average. This would be a point of importance, since practically all the children observed were from poor class homes. Results of the analysis of samples of milk from the various wards of the city were therefore consulted, but it was found that there was no tendency whatever to a lower fat percentage in the poor class districts. The evidence, then, favours the statement that practically all the milk retailed in Glasgow, both in the summer and winter months, contains at least 3 per cent. fat. It has therefore been accepted that if a child under one year were receiving undiluted cow's milk in ample quantity, the fat intake was sufficient: and in children over one year a general diet containing one pint of milk, soup, gravy, or butter was taken as supplying the necessary quota of fat.

In the case of breast-fed children an opinion regarding the sufficiency or otherwise of the diet depended on the history of the health of the mother, her

food supply, and the quantity of the secretion. The fact that the Corporation of Glasgow was supplying free meals to nursing mothers, and cow's milk for the children, was in many cases of considerable help in deciding if a particular diet was fat-sufficient or not.

Source of Material.

The material for this investigation was obtained from the Royal Hospital for Sick Children, Glasgow. The system adopted in this hospital, by which many babies dismissed from the wards are brought to the hospital regularly as out-patients until they are a year old, was of particular advantage in carrying out the study. Some of the babies came under observation at the age of a few weeks. They were seen weekly or fortnightly, weight charts being kept and clinical notes made, and they were radiographed regularly once a month. Written instructions of the diet were given to the mothers, who were questioned frequently, so that although the children were not under direct observation, as in the experiments recently described by Miss Chick (2), one felt fairly sure that the diets prescribed were being given. All those cases were discarded in which there was the slightest doubt on this point.

The Incidence of Rickets in Children on a Fat-sufficient Diet.

In all, 51 children were studied, and of these 27 were artificially fed. All these children were less than ten months old when they came under observation, and some were only a few weeks. Many of the observations extended over a year. In those artificially fed, undiluted cow's milk was the diet employed. This was supplied free of charge through the Glasgow Corporation by a well-known dairy company, in 33 per cent. of the cases: this milk showed a monthly average of 3.3 per cent. fat, and was never less than 3.2 per cent. fat. It might of course be argued that although a sufficiency of milk was ingested it may not have been absorbed. Against such an argument is the absence of all vomiting and diarrhoea, and the presence of a steadily increasing weight-curve. Furthermore, Hutchison (3) has shown that in at least advanced cases of rickets there is no defect in the fat assimilation.

The results have been classified according to whether the children were observed during the summer or during the winter months, and are shown in the following table:

TABLE II. *The Incidence and Severity of Rickets on a Fat-sufficient Diet.*

Season.	No. of Cases.	Nature of Feeding.	No. developing Rickets.	Percentage developing Rickets.	Percentage developing moderately severe or severe Rickets.
Winter {	19	Artificial	17	90	69
	18	Breast	13	72	44
Summer {	8	Artificial	1	12	0
	6	Breast	0	0	0

It will be seen from the above table that of the children observed during the winter months 90 per cent. of those on a fat-sufficient artificial diet developed rickets; and of the breast-fed babies over 70 per cent. developed the disease. The accompanying radiographs (Pl. 12, Figs. 1, 2, and 3) show the average severity of the lesions. The total fat intake in the artificially fed cases is shown in the appendix (No. 1) and a comparison with the ideal fat intake is made. The intake in grammes of fat per kilo of actual body-weight was also estimated in each case, and since most of the children observed were, like the majority of the children from this social class, slightly under the normal weight, the intake in grammes per kilo of body-weight was correspondingly high.

In the summer months, on the other hand, only one child out of 14 developed rickets, and this was after a prolonged illness in hospital.

These experiments differ from those recently carried out by Miss Chick in Vienna (2) in that no cod-liver oil was added to the fat-sufficient diets. It is not improbable, therefore, that the difference in the results is due to some constituent of cod-liver oil other than the fat-soluble A vitamin. It is of interest that, in a few cases where rickets had developed during the first winter of life and had healed during the following summer, a relapse, evident by radiograph, occurred during the second winter, but without any further sign or symptom.

The Incidence of Rickets on a Fat-deficient Diet.

These observations were conducted in exactly the same manner as those just described, but, instead of the ordinary fat-sufficient diet, one definitely deficient in fat was given by prescribing milk mixtures of 1 per cent., 1.5 per cent., and 2 per cent. fat. These were obtained by partly skimming the milk or by diluting with water: the necessary caloric value was reached by the addition of sugar and occasionally of Sister Laura's Food. The diet most commonly employed was Pirquet's so-called 'sibo', made of half milk and half water with the caloric strength of the mixture raised to that of human milk by the addition of sugar. This gives, of course, a mixture of 1.5 per cent. fat and 8.9 per cent. carbohydrate. The cases are divided as before into winter and summer groups, and the following table shows the results:

TABLE III. *The Incidence and Severity of Rickets on Fat-deficient Diets.*

Season.	No. of Cases.	Nature of Feeding.	No. developing Rickets.	Percentage developing Rickets.	Percentage developing moderately severe or severe Rickets.	No. of Doubtful Cases.
Winter {	17	Artificial	12	70	41	1
	4	Breast	3	75	33	
Summer	12	Artificial	1	8	0	2

The percentage developing rickets during the *winter months* is lower than in children observed on a fat-sufficient diet, as is also the percentage of severe or moderately severe cases. In the children remaining free from rickets the diets were

continued for 3 to 4 months. Radiographs of two cases fed for long periods on a fat-deficient diet with no appearance of rickets are shown (Pl. 13, Figs. 4 and 5).

In the *summer months* only one child out of 12 developed rickets, and this was a slight case in a child kept in hospital for a long period for metabolism experiments. This was one of the children in whom a recrudescence of the rachitic condition occurred during the following spring, and that while on a fat-sufficient diet. Practically all the diets were of 1.5 per cent. fat, the amount of carbohydrate was large, varying from 8 per cent. to 12 per cent., and the periods on the diet were long, from three to seven months, and averaging five and a half months.

The Investigation of Diet Histories from Birth of Definitely Rachitic Children with Special Reference to their Probable Fat Content.

Although undoubtedly the most exact information is obtained from the study of cases of rickets developing in children whilst under observation, it was thought that it would at least be of interest to attempt to form some estimate of the previous nature of the feeding and the probable fat content of the diet in cases of definite rickets. Particulars were obtained from the mothers, and great care had to be exercised to get this information as accurately as possible. The same standards of fat-sufficiency as previously laid down were adopted both in the artificially-fed and in the breast-fed children. Many of the children had, at some period, been fed on dried milk or patent foods, and consequently it was also necessary to determine from these the average daily fat intake at the various months.

For purposes of analysis the material in this section of the investigation has been divided into two groups. The first group consists of children of less than 1 year. Many of these children seemed healthy and had come under observation in their earliest infancy for the purpose of circumcision. It was thought that from such a series the age of onset of the disease might be decided. For the second group cases of well-marked rickets in children from 1 to 4 years of age were selected.

Group I. (Children under 1 year.)

Fifty-five babies were radiographed, and of these 28, or 51 per cent., showed definite radiographic evidence of rickets. In 35.7 per cent. of the positive cases the disease was present before six months and in 10 per cent. before four months of age. It is worthy of comment, too, that in many cases of these positive rachitics routine examination gave no suspicion of the disease, and, prior to the X-ray examination and disclosure of its presence, some had been chosen as controls in metabolism experiments. Later on, however, in most of the cases the clinical signs became quite definite.

The following table (No. IV) gives a synopsis of the diet histories in these young babies, and shows that in 78.5 per cent. of the cases the diets appeared to contain a sufficiency of fat :

TABLE IV. *To show Respective Numbers on Fat-sufficient and Fat-deficient Diets in Young Children showing Evidence of Rickets.*

Fat in Diet.	Nature of Diet.	No. of Children.	Percentage.
Sufficient	Entirely breast-fed	4	78.5
	Breast followed by cow's milk	10	
	Entirely on cow's milk	5	
	Full cream Glaxo and cow's milk	2	
	Full cream Glaxo entirely	1	
Deficient	Entirely breast-fed	2	21.5
	Cow's milk in insufficient quantities	2	
	Nestle's milk	2	

Group II. (Children 1 to 4 years.)

These were all children with well-marked rachitic stigmata. The value of these diet histories depends, of course, on the accuracy of the mother's memory, and so the findings have not the same importance as those obtained in Group I; 112 cases were examined, full diet particulars being obtained. The results, which have been subdivided according to whether or not the children had received breast milk in infancy, are shown in the following tables (Nos V and VI):

TABLE V. *Proportion of Rachitic Children receiving Suitable Breast Milk followed by Artificial Sufficient or Deficient Diet.*

No. of Cases.	Duration of Breast-feeding.	Followed by Fat-sufficient Diet.	Followed by Fat-deficient Diet.
	Months.		
17	Less than 3	7	10
13	3	8	5
2	4	0	2
2	5	1	1
3	6	2	1
1	7	0	1
4	8	3	1
7	9	6	1
4	10	4	0
1	11	1	0
17	12	16	1
12	Over 12	9	3
83		57	26
		i. e. 68 %	i. e. 32 %

TABLE VI. *Proportion of Rachitic Children fed from Birth on Artificial Fat-sufficient or Fat-deficient Diet.*

No. of Cases.	Fat-sufficient Diet.	Fat-deficient Diet.
29	11	18

N.B.—In the above tables, if the breast milk is considered to have been deficient, the case is put into the fat-deficient group.

It will be seen from the above tables that, just as in the case of the younger children, the examination of the diet histories of these older rachitics reveals no apparent deficiency of fat in the majority of cases. Of 112 investigated, the diet appeared to have been satisfactory in 68, or 60 per cent. The degree of deficiency

of fat was slight (20 per cent. below the ideal) in 25 per cent., moderate (20 per cent. to 40 per cent. below the ideal) in 30 per cent., and marked (over 40 per cent. below the ideal) in 45 per cent. of the cases.

The disease was severe in 48 per cent. of the children whose diet appeared to have been sufficient in fat, and in 45 per cent. where it had apparently been deficient.

The Effect of various Remedial Measures.

The criteria of improvement. Improvement in the rachitic condition was gauged both by radiographic and clinical evidence. The radiographic signs of healing, recently described in detail by Park and Howland (1), consist in the deposition of lime salts on the epiphyseal side of the transitional zone, the appearance of tooth-like processes extending down from this line, and the gradual increase in length of the bone until all appearance of deficient calcification disappears. *Clinically* the ability of the child to walk unsupported was taken as the most important sign of recovery, although attention was also paid to the eruption of the teeth, decrease in size of the fontanelle, lessening of the epiphyseal enlargements, and to the child's general health.

The strictly logical divisions of the scheme of treatment in testing the fat-soluble A hypothesis should be the effect of treatment, (1) while on a fat-sufficient diet, and (2) while on a fat-deficient diet. As many of the children were of an age when they receive a mixed diet, it would have been a matter of considerable difficulty to arrange a fat-poor diet, but I was able to observe four younger children in which this was possible. In one set of cases large amounts of fat-soluble A-containing substances were given in the form of cod-liver oil and butter, whereas in the others entirely different curative measures were adopted and the previous diet was continued unchanged.

In order that the details of treatment could be more strictly supervised, 34 children were admitted to the Royal Hospital for Sick Children, Glasgow, and 11 of these were treated in the country branch of the hospital. Every effort was made to have these indoor cases as comparable as possible, so far as the severity of the disease was concerned. All these indoor cases were on a general diet containing $1\frac{1}{2}$ pints of milk, gravy, soup, margarine, and 3 oz. of meat, while those receiving cod-liver oil had butter instead of margarine to raise as much as possible the fat-soluble A content of the diet.

The tendency to natural healing during the summer. During the first summer of the investigation it was found that practically all the cases observed, whether being treated or not, and whatever the diet, presented healing, and that at a uniform rate. The single exception to this rule was that of a child living in a sunk flat and never allowed out, the mother being ill. This tendency to heal during the summer months is of course well known, and is usually ascribed by the supporters of the vitamin theory of the aetiology of rickets to the better vitamin content of cow's milk during these months. If this were the case, then the giving of a diet very poor in fat, and consequently reducing the fat-

soluble A vitamin intake, should theoretically inhibit this tendency to spontaneous cure. With this in view four children with definite rickets were put on a 1.5 per cent. fat diet during the summer months. Three of these had no other treatment except that the mothers were advised to take them out to the fresh air as much as possible. The other child received 9 minims of phosphorated oil daily. The average fat intake was about half the ideal. In all, radiographic and clinical improvement was marked and equal, the children on the fat-poor diet alone improving as rapidly as the one getting phosphorus in addition. Radiographs are shown to demonstrate the healing in one of these cases (Pl. 13, Figs. 6 and 7).

From the above findings, it will be obvious that in attempting to estimate the value of various remedial measures the results of treatment during the summer months must be discarded; the following remarks, therefore, apply only to cases treated during the winter.

Methods of Treatment adopted and Results.

1. *Cod-liver oil.* Norwegian cod-liver oil was used, this being supplied by the hospital, and care was taken that the out-patients received the supply regularly. Treatment was commenced with 3 drachms of oil and increased until the children were receiving 1 oz. daily. The children treated in hospital were kept in their cots, so that, to a certain extent, their exercise was limited. In all, 13 cases were treated. The diet given to the indoor cases has been described above, a daily allowance of butter being given. For the out-patients the diet remained unchanged.

Radiographic results. Definite improvement occurred in 91 per cent. of the cases if treatment extended to two months or more. Slight improvement was usually noted after one month's administration, but it was not until after a period of two months that healing was definite, and the average time required in severe cases to obtain normal bones was five months.

In four cases phosphorus was added to the cod-liver oil, but with no apparent increase in the rate of healing.

In some cases improvement was slight, and a radiograph is shown of a child (A. S.) who, after constant administration of cod-liver oil for six months, still showed severe rickets (Pl. 14, Fig. 8).

The improvement was most uniform in those cases treated as in-patients, and those in hospital improved just as rapidly as those treated in the country branch.

Clinical results. These were disappointing, and the clinical improvement was not nearly so marked as the radiographic.

Of the indoor patients 20 per cent. walked alone in $3\frac{1}{2}$ months or more, whilst 46.6 per cent. showed only slight improvement even after periods extending in one case to seven months.

The improvement was most marked in children treated as out-patients.

2. *Massage.* In all, 22 cases were treated, 6 in hospital, 3 in the country

branch, 7 at the out-patient department, and 6 in their own homes. The children treated in the hospital, country branch, and at the out-patient department had the legs massaged for half an hour three times weekly, whilst the mothers of those treated at home were shown how to apply the massage, and were instructed to sponge the legs with cold water morning and evening and then to rub the legs vigorously for a quarter of an hour. In all instances the children were kept on their feet as much as possible and encouraged to walk. The diet for the indoor cases has been described above, margarine being given instead of butter. The diet of the out-patients remained unchanged.

Radiographic results. The improvement as evidenced by radiograph was as a rule slight or entirely absent. In 25 per cent. of the cases the improvement was slight. In two cases, however, the improvement was definite (Pl. 14, Figs. 9 and 10).

There was no significant difference between the results obtained in the three groups (out-patients, in-patients in hospital, and in-patients in the country branch).

Clinical results. Improvement was much more marked and more constant than in those cases treated with cod-liver oil.

Twenty per cent. of the indoor cases, all of whom were severe examples, walked alone in two months. In only 33 per cent. of the indoor cases was the improvement slight.

Of seven cases treated at the out-door department 100 per cent. walked unsupported in three to six weeks.

Treatment by massage at the out-patient department. The results in this group are so striking that a slightly more detailed description may be permissible. The massage was given by the Sister in charge of the Medical Department, and the mothers were instructed to continue the massage at home between the visits, and to 'keep the child on his feet'. All the cases were severe, and the results were uniformly good, the average period before the children were walking alone being one month. Moreover, the improvement in the general health was as marked as the improvement in the 'rickets'. It is of interest that very frequently no radiographic improvement accompanied this marked clinical progress. Dr. Leonard Findlay (4) has already reported a series of cases treated in this way, and the results detailed above correspond very closely with his. No increased tendency to ensuing deformity as the result of this treatment was ever observed.

3. *Violet rays.* It had been hoped to treat a fairly large number of children by this method during the winter months, but unfortunately several of those selected for treatment developed measles, and this material was lost. In one case only was the method given a really fair trial in the winter, and in this child the radiographic improvement was marked and there was also definite clinical improvement. This radiographic improvement was well marked in two months and was quite as definite as that obtained with cod-liver oil.

4. *Controls.* Nine children were observed untreated during the winter. These were out-patients, and, except for a 'placebo' of sodium bicarbonate, no

treatment was instituted, and the diet remained unaltered. In no case was there definite radiographic or clinical improvement.

Discussion.

It is necessary now to bring together the results obtained in the various parts of the investigation and to consider whether they lend support to the theory that rickets is a deficiency disease due to a deficiency of the fat-soluble A vitamin in the diet. The results in the divisions of the investigation have been:

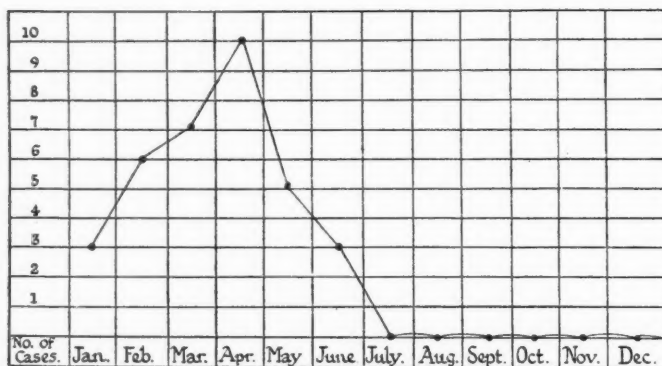
- A. 1. 90 per cent. of the children observed during the winter months on an artificial fat-sufficient diet, and 72 per cent. of the breast-fed babies in cases where the milk fat appeared to be present in its normal amounts, developed rickets.
2. 12 per cent. of the children observed in the summer months on an artificial fat-sufficient diet developed rickets.
- B. 1. 70 per cent. of the children observed during the winter months on an artificial diet poor in fat, and 75 per cent. of the breast-fed babies in cases where the milk fat appeared to be deficient, developed rickets.
2. Only 8 per cent. of the children observed in the summer months on an artificial diet poor in fat developed the disease.
- C. 1. The investigation of the diet of 28 young babies with radiographic evidence of rickets revealed no deficiency in the fat content in 78.5 per cent. of the cases.
2. The investigation of the diet histories of 112 older children with well-marked rickets showed no fat deficiency in 60 per cent. of the cases.
- D. Although the giving of cod-liver oil, and therefore of the fat-soluble A vitamin, certainly influences the calcification of rachitic bones more surely than does any other method, with perhaps the exception of violet rays, in some instances the response was poor. Moreover, bone healing was produced by measures such as violet rays and massage, which have no apparent connexion with the fat-soluble A vitamin. Since healing was observed to occur on diets very deficient in fat, it seems probable that the potent factor in cod-liver oil is not the fat-soluble A vitamin but some other substance, as suggested by McCollum and others (5).

The above results therefore strongly oppose the theory that rickets is a disease essentially of dietary origin, and, in particular, that it is due to a deficiency of fat in the diet. But it might be said that although the diets given, on which children were observed to develop rickets, contained a sufficiency of fat, it was not proved by growth experiments on animals that the fat-soluble A vitamin was present, and that rickets may still have been due to a deficient supply of this vitamin. In favour of this the marked seasonal incidence of the disease could be brought forward, because it has been shown (6) that cow's milk contains less of the fat-soluble A vitamin in the winter months, when the cows

are stall fed, than in the summer months when they are at pasture. From a graph (see below) showing the seasonal incidence of the disease in the cases under observation it is seen how the radiographic signs invariably appeared during the late winter and early spring. Against this view that the seasonal incidence of the disease is due to the seasonal variation of the fat-soluble A vitamin in cow's milk, one may quote the work of Hess (7). Hess, by feeding one group of children on dried milk from pasture-fed cows (vitamin rich) and another group on milk from stall-fed cows (vitamin poor), found no difference in the incidence of rickets in the two groups. And further, if rickets were due to a comparative lack of vitamin in cow's milk during the winter months, the child in the better class family, whose milk supply is the same as that of his poorer class brother, should develop the disease in exactly the same way, which we know is not the case. It cannot be because the better class child received more

The Seasonal Incidence of Rickets.

Graph to show Month of Radiographic Development of Rickets in Children actually under Observation.



N.B.—Two of the cases developing in June were children in hospital after an acute illness.

milk and therefore more vitamin, because an ample supply of milk was given to the children (all of the poor class) in the present experiments. Nor would this difference in vitamin content account for the cause of rickets observed in the breast-fed babies of mothers on a good general diet. It may, then, be said that the diet of the poor class child contains a large amount of carbohydrate, and that it is the excess of carbohydrate, together with the deficiency of vitamin, which produces rickets. But amongst the children observed by the author, the incidence of rickets in those fed on a poor fat diet with large amounts of carbohydrate was less than in those on a full diet with only small amounts of carbohydrate: and in the summer the incidence of rickets on a poor fat but rich carbohydrate milk mixture was very low indeed.

It does not, therefore, seem possible, in view of these facts, to correlate the seasonal incidence of rickets with the seasonal variation of the fat-soluble A vitamin content of cow's milk.

Summary and Conclusions.

The evidence in this investigation is strongly opposed to the theory that rickets is produced by lack of the fat-soluble A vitamin in the diet, because :

1. Cases of severe rickets occurred in children under observation on a diet, whether natural or artificial, which contained the normal amount of fat. Deficiency of fat in the diet cannot, therefore, be an indispensable factor in the production of the disease. As the diets were well balanced, and did not contain an excess of carbohydrate, an improper diet or an excess of carbohydrate does not appear to be a necessary aetiological factor.

2. The percentage of children developing rickets under observation was lower, both in summer and winter, in those fed on a fat-poor diet than on a fat-rich diet. In the summer months 76 per cent. of the children fed for long periods on a diet very deficient in fat remained free from any suspicion of rickets. Lack of fat, therefore, does not necessarily lead to rickets. As these diets contained large amounts of carbohydrate, excess of carbohydrate does not appear to predispose to rickets. The summer incidence of rickets is low.

3. An examination of the diet histories of 28 young rachitic babies showed that the disease had occurred on a large variety of diets, 78.5 per cent. of which appeared to have been fat-sufficient. Of 112 older rachitics the diet histories in 60 per cent. of the cases showed no indication of any deficiency of fat. 30 per cent. of these children had been breast-fed to ten months or more. Furthermore, the percentage of severe cases was slightly higher in the fat-sufficient than in the fat-deficient group; this, it will be recollected, was also the case in the series of children deliberately fed on fat-sufficient and fat-deficient diets (see pp. 323 and 324). In short, rickets was found to have developed on almost any diet, whether the indiscriminate one given by the careless mother or the well-balanced one of the careful mother.

4. Marked spontaneous healing of bones and clinical improvement was observed during the summer months. Healing progressed in the summer months in children on a diet whose fat-soluble A content must have been extremely low. The following winter results are recorded: definite radiographic improvement nearly always follows the administration of cod-liver oil. The average period required to obtain normal bones was five months. Some cases, however, resisted treatment. Clinical improvement with cod-liver oil was often slight, and was not commensurate with the radiographic improvement. Definite radiographic improvement occurred with measures such as violet rays or massage, which would appear to be in no way connected with the fat-soluble A vitamin; and the most marked clinical improvement was obtained with massage.

I have much pleasure in recording my gratitude to Dr. Leonard Findlay for suggesting this work, putting clinical material at my disposal, and for many valuable suggestions and helpful criticisms. I have also to thank the staff of the Radiographic Department of the Royal Hospital for Sick Children, Glasgow, for the large series of excellent radiographs taken by them. To Sister Elinor of the Out-patient Department of the same Hospital, my thanks are due for collecting much of the clinical material used, and for her patience and enthusiasm in the massage treatment which she undertook. Finally, I have to thank the Medical Research Council, by whom the expenses of this research were borne.

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APPENDIX I.

Table comparing the ideal fat intake with that observed in children who developed rickets on a fat-sufficient diet.

Month.	Ideal Fat-in-take in gm.	M. H.	A. C.	D. W.	A. H.	C. McG.	A. G.	J. M.	J. C.	J. Con.	J. R.	H. D.	A. Hol.	J. Coy.	A. Q.	A. N.	J. H.	J. McK.
1	18.0	Glaxo	breast	Glaxo	breast	Glaxo	breast	breast	breast	breast	whole milk	whole milk	breast	breast	whole milk	breast	not known	*
2	21.0	"	Glaxo	Glaxo	Sister Laura's food	"	"	"	"	whole milk	whole milk	"	Allen-Sister Laura's No. 1 food	"	"	"	"	"
3	23.0	whole milk	21.6	Sister Laura's food	24.3	22.5	27.0	22.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0
4	25.0	"	22.5	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0
5	26.3	20.7	22.5	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0
6	27.8	23.4	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0
7	28.0	27.0	28.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0
8	29.7	28.8	31.5	28.8	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5
9	30.25	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5
10	30.7	24.0	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5
11	31.6	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5
12	32.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5	31.5
13		31.5		1 pint milk, butter, gravy														
14		31.5																
15		R																
16																		
17																		
18																		

R = month of development of rickets (radiograph).

R² = rickets at 1½ after deficient diet. Healed and recurred at 1½ on sufficient diet.

* = rickets at 1½. Healed and recurred at 2½ on diet of 1 pint milk, margarine, meat, soup, and gravy.

APPENDIX II.

Table comparing the ideal fat intake in grammes with that observed in children remaining free from rickets on a low fat diet.

Month.	Ideal Fat In- take in gram.	Winter.				Summer.						Doubtful Cases.			
		M.A.	A. L.	J. S.	T. W.	F. M.	E. F. M. McM.	T. W.	C. L.	R. W.	S. D. R. McP.	J. P.	M. H.	M. S.	J. S.
1	18-0				13-5										
2	21-0				13-5										
3	23-0			7-2	13-5		Nestlé's milk				12-6	Nestlé's milk	16-65	12-6	Nestlé's milk
4	25-0			7-2	13-5			11-7	12-6	16-2	9-45	12-6	22-5	12-6	"
5	26-3			7-8	21-6	7-2	15-75	13-5	13-0	14-4	12-6	13-4	13-7	13-5	"
6	27-8		22-8	9-0	21-6	7-2	15-75	17-5	14-2	16-2	15-75	14-2	?	17-5	15-75
7	28-0		22-8	neg. ¹	31-5	7-2	15-75	19-8	16-8	16-2	15-75	16-0	15-75	18-9	16-65
8	29-7	18-9	13-5		31-5	neg.	18-9	21-6	18-9	16-2	19-8	16-0	18-0	18-9	16-65
9	30-25	18-9	18-0		21-0		18-9	21-6	18-9	neg.	19-8	16-0	20-25	18-9	16-65
10	30-7	15-75	15-75		21-0		22-5	15-75	18-9	neg.	neg.	neg.	?	20-25	16-2
11	31-6	15-75	18-0		31-5		neg.	15-75	27-0	18-9	neg.	neg.	?	?	22-6
12	32-5	20-0	24-0		neg.		18-0	15-75	neg.					?	?
13		neg.	neg.			neg.	neg.	neg.							
14															
15		neg.	neg.		neg.		neg.	neg.							
16															
17															
18															

neg. = negative radiograph.

¹ This was a case of congenital obliteration of the bile ducts and fat absorption was very deficient.

Note.—For sake of brevity the fat intake in those children developing rickets on a lard fat diet is not given: the average intake in these cases proved to be slightly higher than in those remaining free from rickets.

APPENDIX III A.

Diet of Babies showing Radiographic Evidence of Rickets.

A. Fat-sufficient.

Name.	Age.	Diet.	Degree of Rickets.
	months		
1. John Adams	8	Breast to 3/12, when W.M. 2 to 3 pints	Moderately severe
2. Henry Bryan	6	W.M. 16 to 20 ounces. (Weight = 5.2 kilos)	" "
3. Joan Kerr	9	Breast to 3/12, when Sister Laura's food with W.M.	" "
4. Jane Newlands	10	Breast to 2/12. Glaxo (F.C.) and W.M. 10 ounces. Cod-liver oil 3 drachms daily from 9/12	" "
5. Francis Taylor	4	Breast to 2/12. Then Sister Laura's food with W.M.	" "
6. Edward Wallace	7	Breast only (2.4 per cent. fat)	Severe
7. Joseph Agnew	13	Glaxo (F.C.) to 6/12. Then W.M. 2 to 3 pints	Definite
8. James Brady	4½	W.M. 2 pints	"
9. John Coletta	6	Glaxo to 3/12. Then W.M. 2 pints	"
10. Mary King	9	Breast only	"
11. Archibald McCrae	7	Breast to 2/12. Sister Laura's food with W.M.	"
12. Hugh McGuire	8	W.M. 1 pint. By 6/12, 1½ pints, and then 2 pints	"
13. Matilda McEwan	12	Breast only (2.9 per cent. fat)	"
14. John McKinney	5	Glaxo (F.C.)	"
15. James Wilson	3½	Breast to 14 days. Then W.M. 1 pint. (Weight = 4 kilos)	"
16. Margaret Paterson	10	Breast to 9 months. Then W.M. 2 pints	"
17. George Syme	10	Breast to 2/12. Sister Laura's food with W.M. to 3/12. Then 2 pints W.M.	"
18. David Wallace	10	Breast to 2/12. Sister Laura's food with W.M. to 3/12. Then 2 pints W.M.	"
19. Laurence Lawson	9	W.M. 2 pints	"
20. William Lang	6	Breast to 6 weeks. Then Sister Laura's food with W.M.	Slight
21. James Milligan	7	Breast to 6 weeks. Then W.M. 2 pints	"
22. James Simpson	4½	W.M. 1½ pints	"

B. Fat-deficient.

1. John McGregor	3½	Breast (1.1 per cent. fat)	Moderately severe
2. Charles Boyd	11	W.M. about 1 pint	Definite
3. Margaret Dally	8	Breast (food scarce) supplemented from 5½/12 with W.M. 6 ounces	"
4. Edward Murray	4	W.M. 1 pint to 2/12. Then Nestlé's milk	"
5. Violet O'Rourke	11	Breast to 3/12. Then W.M. up to 1½ pints	"
6. Jessie Muir	11	Allenbury No. 1 to 4/12. Nestlé's milk to present	Slight

Note.—In all cases Sister Laura's food given with W.M. according to directions.

APPENDIX III B.

Details of Diet in Investigated Cases.

Average normal daily fat intake up to 1 year is taken as:

1st month,	0.18 grm.	6th month,	27.0.	1 year,	30.0 grm.
3rd "	22.5 grm.	10th "	30.0.		

Name.	Age at 1st Observation.	Diet.	Severity of Rickets.	Fat-sufficiency.
	years			
1. John McLennan	11/12	Breast to 3 months. Then Sister Laura's food and W.M. according to directions	Slight	Sufficient
2. Jeanie Paterson	11/12	Breast to 3 months. Then Sister Laura's food and W.M., plus an extra pint of W.M.	Moderate	"
3. George Smith	1 8/12	Breast to 3 months. W.M. 2 pints, with bread and butter and milk pudding to 1 5/12 yrs., when soup and gravy added	Severe	"
4. Jack Green	10 1/2/12	Breast to 3 months. Sister Laura's food and W.M. to 9 months, then added bread and butter, soup, gravy, mince, 1/2 pint milk	Moderate	"
5. Walter Elliot	1 9/12	Breast to 3 months. Sister Laura's food and W.M. to 1 2/12 yrs. Then general diet, with gravy, soup, egg, margarine, 1/2 pint milk	Severe	"
6. Peter Forisky	1 5/12	Breast to 3 months. W.M. 2 pints to 1 year (also 'Virol' from 7th to 10th month). Then general diet, with butter and margarine (half of each), gravy, soup, egg	Moderate	"
7. Patricia Warnoch	2 10/12	Breast to 3 months. Robinson's barley, with 2 pints W.M. to 1 year. General diet, with butter, soup, gravy, 1/2-1 pint milk. Scott's emulsion 1 6/12 to 1 9/12	Severe	"
8. Margaret Tooley	2	Breast to 3 months. Sister Laura's food and W.M. to 8 months. Glaxo (full cream) to 1 year, when supplemented with bread and butter. At 1 3/12 soup, gravy, general diet	Moderate	"
9. Patrick Crossan	1 4/12	Breast to 5 months. In Belvedere Hospital to 7 1/2 months. W.M. 1 pint and Allenbury's food and W.M. to 1 year 3 months. Then 1 pint milk, soup, gravy, mince	Moderate	"

Details of Diet in Investigated Cases (continued).

Name.	Age at 1st Obser- vation. years	Diet.	Severity of Rickets.	Fat- sufficiency.
10. Stewart Armour	2 10/12	Breast to 6 months. Full cream Glaxo to 1 year. Then general diet, with butter, soup, gravy, and at least $\frac{1}{2}$ pint milk	Severe	Sufficient
11. James Campbell	1 1/12	Breast to 6 months. W.M. (about 2 pints), with milk foods and bread and butter	Moderate	"
12. Margaret McGregor	1 2/12	Breast to 8 months. W.M. 32 ounces to 1 1/12. Then Benger's food added	Severe	"
13. Agnes Miller	1 10/12	Breast to 8 months. W.M. 2 pints to 1 year, supplemented by porridge from 10 months. Then general diet, with butter, soup, and gravy	Severe	"
14. Allan Cassidy	3	Breast to 8 months. Then gradually ordinary diet, with 1 pint milk, soup, gravy, and margarine	Moderate	"
15. Mary McKellar	1 9/12	Breast to 9 months. Then $1\frac{1}{2}$ pints W.M., with soup, gravy, egg, margarine	Moderate	"
16. Philip Dally	2	Breast to 9/12, supplemented from 3 months with full cream Glaxo. Then $1\frac{1}{2}$ pints milk, with puddings and milk to 1 year, when gravy, soup, 1 pint milk, margarine	Severe	"
17. Robert Warnoch	1 2/12	Breast to 9 months. Then 1 pint milk, butter, soup, and gravy	Slight	"
18. Peggy McPherson	4	Breast to 9 months. In fever hospital for 1 month. Then general diet, with $\frac{1}{2}$ pint milk, soup, gravy, egg, butter, and margarine (half and half)	Moderate	"
19. Jessie Lawson (twin)	2	Breast supplemented by 1 pint W.M. to 9 months. Then general diet, with 2 pints W.M., margarine, soup	Severe	"

Details of the diet in some of the cases where it was considered to be deficient in fat are given below:

Name.	Age at 1st Obser- vation. years	Diet.	Degree of Rickets.	Fat- sufficiency.
1. Alex. Ramsay	1 7/12	Breast to 3 months. 1 pint milk to 10 months, when milk pudding and egg added. At 1 year, butter, gravy, soup	Moderate	Deficient 3rd to 10th month
2. George Timothy	5 2/12	Breast to 1 5/12 yrs. Milk plentiful, but mother's diet poor. Followed by general diet, with soup, gravy, and margarine	Severe	Deficient to 1 5/12

Details of Diet in Investigated Cases (continued).

Name.	Age at 1st Obser- vation. years	Diet.	Severity of Rickets.	Fat- sufficiency.
3. Mary Thompson	2 2/12	Nestlé's milk to 1 year. Then general diet, with butter, $\frac{1}{2}$ pint milk, gravy, and soup	Severe	Deficient to 1 year
4. Neil Turpie	3 10/12	Breast to 8 months. Allenbury's No. 1 food to 1 year, when general diet, with soup, gravy, and margarine	Severe	Deficient 8th month to 1 year
5. Sarah Anderson	3 10/12	Savory & Moore's food to 1 year. Then general diet, with soup, gravy, and butter	Severe	Deficient to 1 year
6. Lenita Rossi	1	Breast to 5 months. 1 pint milk to 8 months. Then $1\frac{1}{2}$ pints to 1 year. Scott's emulsion 10th to 12th month	Moderate	Deficient 5th month to 1 year
7. Margaret Boyle	1 10/12	Not more than 1 pint milk to 6 months. Then 2 pints to 1 year, when general diet, with soup, butter, and gravy	Moderate	Deficient to 6 months
8. Robert McKendrick	1 1/12	Half cream Glaxo to 3 months. Then Savory & Moore's food, with 2 pints milk to present	Slight	Deficient to 3 months
9. Christina Johnstone	1 7/12	W.M. 16 ounces to 3 months. Sister Laura's food to 1 year. Then $1\frac{1}{2}$ pints milk, butter, and milk puddings		Deficient to 3 months

Examples of Rickets developing during the Winter on a fat-sufficient artificial diet.



FIG. 1. D. W. 1 yr.



FIG. 2. 13/12.

Example of Rickets developing while on the breast (fat-sufficient).



FIG. 3. E. W. 7/12.

Radiographs negative for Rickets after a period of fat-deficient diet feeding.

Winter

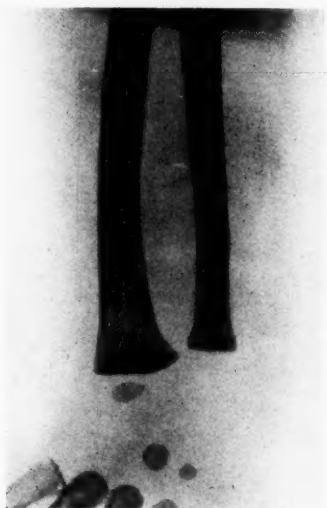


FIG. 4. A. L. 1 year.
After a diet period
of 7 months.

Summer



FIG. 5. C. L. 10/12.
After a diet period
of 7 months.

Healing during the Summer on a fat-deficient diet.



FIG. 6. E. C. 10/12, 5. v. 22.



FIG. 7. 19. ix. 22 (aet. 1 2/12).



Poor response to cod-liver oil treatment.



FIG. 8. A. S. 2 8/12.

Radiograph taken after administration of cod-liver oil (3 T. T. i. b.) for 6 months.

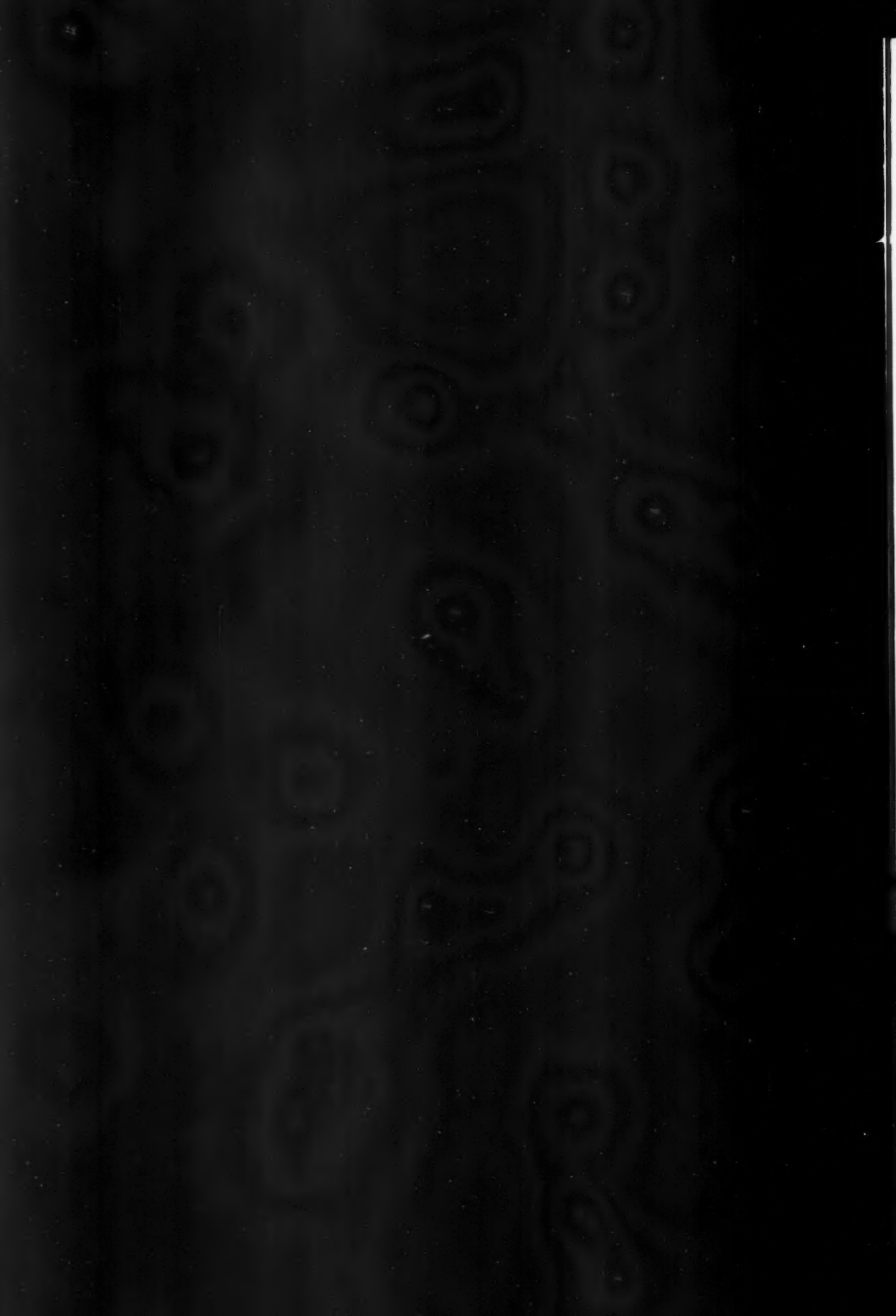
Radiographic improvement with massage alone (Winter).



FIG. 9. 14. ii. 22.



FIG. 10. 14. iv. 22.



ON THE PHOSPHORUS AND CALCIUM OF THE BLOOD IN RENAL DISEASE

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Introduction.

THOUGH recent biochemical work has added very considerably to our knowledge of the types of functional failure which we may encounter in nephritis, and has enabled us to arrive at a fairly accurate estimate of the degree of damage in any particular case, the correlation of the chemical findings with the symptoms of the disease is as yet far from complete. It is true that a relationship, possibly causal, has been established by French workers between the oedema of renal disease and salt retention, and that certain symptoms have been attributed to the presence of an acidosis: but the chemical investigation of the blood and urine in renal disease has been largely concerned with the estimation of certain constituents, which, though they afford us interesting information as to the degree of functional impairment present, are probably not of themselves of great importance in the causation of the symptoms associated with renal failure. The study of the excretion and retention of certain nitrogenous metabolic products—urea, uric acid, and creatinin—bulks largely in the literature of nephritis. The evidence that these bodies are in themselves toxic is but slender. The majority of observers have been unable to demonstrate any toxic effects of urea, and there is no doubt that extraordinarily large doses, about one per cent. of body-weight, are necessary to produce death in animals. Hewlett, Gilbert, and Wickett (1) were able to produce headache, dizziness, drowsiness, and fatigue in human subjects by raising the blood urea to 160 or 245 mg. per 100 c.c., by oral administration of 100 grm. urea. Nausea and vomiting, symptoms pre-eminently associated with uraemia, did not, however, result, and the subjectivity of the toxic effects noted by these observers makes it difficult to exclude altogether the element of suggestion. On the other hand, it is not unusual to meet with patients suffering from obvious uraemia, in whom the blood urea is considerably below the above-quoted figures. The part played by urea in the production of the symptoms of uraemia is therefore doubtful: that the other nitrogenous metabolites, uric acid and creatinin, can cause the symptoms of renal failure has, as far as I am aware, never been suggested. From this aspect,

then, our means of prognosis in renal disease remain in a sense indirect. By determining the degree of failure of excretion of certain apparently non-toxic bodies, we estimate the degree of renal damage, and the resulting probability of retention of toxic substances.

Turning from these nitrogenous bodies to the comparatively unexplored field of the inorganic constituents of blood in renal disease, we find that variations are known to occur in the phosphate and calcium content, which may possibly show a more direct relationship to the clinical symptoms. The estimation of these two bodies and of the urea is possible in about 20 c.c. of blood, a quantity readily obtainable in human patients, while the technique involved is relatively simple and rapid, and therefore suitable for clinical work. Since comparatively little work on the subject has as yet appeared, the literature may be briefly summarized.

The first demonstration of changes in the phosphate content of the blood in nephritis we owe to Greenwald (2), who, in 1915, showed that the acid soluble phosphorus of the serum was frequently increased in renal disease. This rise in the blood phosphates was associated with defective excretion, and was to some extent independent of nitrogenous retention. Generally speaking, however, a raised phosphorus content was accompanied by an increase in the non-protein nitrogen of the blood. Unfortunately this paper contains practically no clinical details. Marriott and Howland (3), who studied the blood phosphate from the standpoint of the acidosis of renal disease, found no constant relationship between phosphate and nitrogen retention. They concluded that the increase in phosphate was sufficient to account for the diminution in the alkaline reserve of the blood, as estimated by the fall in the plasma bicarbonate. The acidosis itself, however, did not appear to be the cause of death. 'The acidosis may be overcome by alkali therapy, but it is a matter of experience that little besides this is accomplished. The disease usually progresses to a fatal termination. Administration of alkali generally fails to bring about a marked reduction in the phosphate.' These authors give some extraordinarily low values for serum calcium in nephritis, as estimated by their own method. In some instances values as low as 1 mg. per 100 c.c. were found. They refer the diminution in the calcium to the excess of phosphate in the blood, since it has been repeatedly shown that administration of phosphates produces increased elimination of calcium mainly via the intestine. Denis and Minot (4), using Bloor's method, have also studied phosphate retention, from the standpoint of blood analysis. Of sixty-eight cases of cardio-renal disease, two-thirds showed definite evidence of phosphate retention. Their figures show no very definite parallelism between phosphate and nitrogenous retention, nor could they find a relationship between the decrease in the alkali reserve and the rise in the plasma phosphate.

Halverson, Mohler, and Bergheim (5), who worked with their own method, have also found low calcium values in nephritic sera. Their figures are, however, considerably higher than those of Howland and Marriott, their minimum value being 6.8 mg. per 100 c.c. of serum. The administration of calcium

lactate by mouth was followed in their cases by a definite rise in the serum calcium, but the connexion was doubtful, since control cases, in which no calcium was given, showed similar increases.

It would appear to be proved, therefore, that nephritis is one of the few diseases in which the serum calcium may be definitely diminished. The extent of this fall is disputed, and its significance in producing symptoms has not been investigated. It is suggested that the calcium fall is the result of an excessive excretion of calcium phosphate by the bowel to compensate for the defective renal elimination. Telfer (6), however, in a recent article, concludes that such excretion of phosphorus by the intestine is doubtful. An increase in the inorganic phosphorus of the blood has been found in a considerable proportion of nephritic cases by the few authors who have studied the point. The connexion between nitrogenous and phosphate retention is uncertain, since, though they frequently occur together, they may apparently accumulate independently.

Lastly, both Denis and Minot, and Marriott and Howland, find that phosphate retention is of bad prognostic import.

Methods.

For the estimation of the inorganic phosphorus of the plasma the method of Bell and Doisy (7), as modified by Lehmann, has been utilized. In this modification a double strength ammonium molybdate solution is used, and the possibility of error due to excessive amounts of oxalate, noted by Denis and von Meyenburg, appears to be largely obviated. The oxalate has, however, been limited to less than 2 mg. per c.c. of blood.

The patients were bled at least three hours after food, in order to eliminate as far as possible the immediate influence of food in raising the plasma phosphate. The plasma was separated from the corpuscles by centrifugalizing immediately after bleeding, since migration of phosphate from corpuscles to plasma occurs on standing. In any estimations of the phosphate content of the blood, plasma is obviously preferable to whole blood, since the phosphate is very unequally distributed between plasma and corpuscles. The excess of phosphate present in the corpuscles, together with the marked variations in the ratio of corpuscles to plasma that are found in renal disease, render the use of whole blood undesirable. Any possible error due to the inclusion of the 'acid soluble phosphorus' in the inorganic phosphate, as estimated by this method, would be so small as to be of no clinical significance, and there is indeed considerable doubt whether such a phosphorus fraction actually exists. In seventeen adult female out-patients, the average inorganic phosphorus content of the plasma, under similar conditions, was found to be 2.99 mg. per 100 c.c. with extreme values of 2.15 and 3.98—a figure which agrees with that found by Bloor, utilizing his own nephelometric method (8).

Calcium. In view of the criticisms of Lyman's method which have appeared, and of the discordant results which it appears to have given in the hands of different workers, this method has not been employed. Incineration methods are lengthy and difficult, and the most simple and rapid method available appears to be that of direct precipitation from the diluted serum with ammonium oxalate. Clarke (9), in a recent review of methods of estimating the serum calcium, concludes that direct precipitation is feasible, and I have therefore utilized the method suggested by Kramer and Tisdall (10). At least one hour has been allowed for the precipitation, however, instead of the half-hour suggested in the original method. The final permanganate titration has been carried out, as far as possible, under the same conditions of speed and temperature, and the permanganate has been frequently titrated against fresh standard oxalate. Wherever possible 2 c.c. of serum were used, and all determinations were made in duplicate. The agreement between duplicates has been good, and the method gives results which compare favourably with the usually accepted values. In seventeen normals an average value of 9.9 mg. per 100 c.c. of serum was obtained, with extremes of 9.3 to 10.5.

Urea was estimated by the well-known urease method of Marshall and van Slyke, which need not be discussed here.

Solids of serum. The serum was allowed to separate in a tightly corked tube, spun out, and weighed on a torsion balance. The slips were then dried at 100° F. to constant weight, all weighings being made as rapidly as possible in order to avoid errors due to evaporation or absorption of water. All determinations were made in duplicate and averaged. The percentage of solids in normal sera was found to lie between 9 and 10 per cent.: figures above 10 were rare, the highest seen in a healthy individual being 10.3. The solids were determined with a view to arriving at some estimate of the extent of blood dilution present, that is, the degree of hydraemia. It is, of course, recognized that in cases in which marked accumulations of waste products occur, such dilution would be to some extent masked; but even in extreme instances of retention the accumulation of waste products would not apparently produce a rise in the serum solids of more than 1 per cent., while grades of dilution are seen, in cases with marked oedema, in which the total solid percentage may fall to 6 per cent. or even lower.

The urea concentration test (Maclean and de Wesselow) (11) was carried out in the morning before the patient had received any fluid. The test was always run for three hours, as the highest concentration is not infrequently obtained during the third hour, especially in cases in which there is reason to suspect delayed absorption. The urea was estimated by hypobromite, a method which is sufficiently accurate for the purpose in view. The great difficulty of the test lies undoubtedly in the diuresis which may occur, if there is much 'free' fluid available in the body for excretory purposes. Cases in which more than 100 c.c. of urine were passed per hour were therefore discarded, since, under such conditions, the kidney takes the path of least

resistance, and a true picture of its concentrating capacity is not elicited. If the patient is taken in the early morning, however, ten hours or more after the last ingestion of fluid, comparatively little free water is available, and a satisfactory test can nearly always be run, the excretion of urine in the second and third hours being usually in the neighbourhood of 50 c.c. per hour. In the patients in whom the blood urea was at a level of 90 mg. per 100 c.c. or over, no urea was administered, but the urea concentration in the corresponding urine was taken as the rough equivalent of the test. With higher levels of blood urea, this comparison gives an unduly favourable picture of the renal efficiency, since under such conditions the kidney is working at a great advantage. For instance, a urinary concentration of 1 per cent. urea with a blood urea of 500 mg. per 100 c.c. actually represents a lower grade of concentrating power than a 0.5 per cent. concentration in the urine with a blood urea at 100 mg. In what is now a considerable experience of the test, it has been found that a dose of 15 grm. of urea will almost always, under the stated conditions, raise the urinary urea concentration in healthy young adults to 3 per cent. and upwards. This is not, of course, the maximum concentration of which the human kidney is capable—a maximum which can only be brought out under such exceptional and unpleasant conditions as those formulated by Ambard (12). During the course of this work a urea concentration of the order of Ambard's maximum has been encountered on one occasion only: in this patient the concentration of urea in the urine amounted to 5.1 per cent. though the blood urea content was only 43 mg. per 100 c.c. A high obstruction of the bowel was present, with persistent vomiting and great depletion of the body fluids. As the result of this loss of water, less than 100 c.c. of urine were passed in the twenty-four hours, and the concentrating power of the kidney was being exerted to the uttermost. The constancy, however, with which in health, even under the comparatively rough conditions of the test, a concentration of 3 per cent. and upwards is obtained, is surprising. The test, while it affords us no information as to the amount of renal tissue functioning, undoubtedly gives a most valuable indication of the concentrating capacity of the organ taken as a whole.

Material.

The available material consisted of 74 patients, all of whom showed protein in the urine. Of these 40 were suffering from nephritis of various types, 25 were cases of albuminuria of pregnancy, in some of which a history of pre-existing nephritis was obtained, and the remaining 9 patients had been admitted to hospital for various surgical affections of the urinary tract, or for cardiovascular disease.

Cases of nephritis may be classified on various lines, clinical, histological, or functional. In view of the fact that only 10 cases ended fatally, the histological classification was impossible. On the other hand, a classification along

the lines of functional failure gives possibly too narrow a view. The cases have therefore been divided into acute, subacute, and chronic, from a consideration of the clinical findings, the history, and, when possible, the post-mortem examination. These groups are further subdivided on the chemical findings into their functional classes—azotaemic, hydraemic, and mixed—oedema being accepted as evidence of the second type of functional failure without any attempt to determine the chloride or water balance. The majority of acute cases were probably instances of acute glomerulo-nephritis, and in many of these a history of a recent throat infection was obtained.

In all 142 complete examinations on the above lines have been made, but of these only a certain number of representative cases are included in the tables. Though the diastatic index was determined by Wohlgemuth's method in all cases, these indices are omitted, since on the whole they throw little light on the condition, and the method itself is open to criticism.

The phosphate findings are given as milligrams of inorganic P per 100 c.c. of plasma, urea as milligrams of urea per 100 c.c. of blood, and calcium as milligrams of Ca per 100 c.c. of serum. Under the heading U.C.T. the maximum concentration per cent. of urea obtained under the conditions of the urea concentration test is given. When, owing to the existence of a high blood urea, no dose of urea was given, the figures under this heading are enclosed in brackets. The blood pressures are systolic pressures estimated by the auditory method. The solids of serum are given in percentages.

The Phosphate Content of the Blood in Renal Disease.

If the extreme upper limit of the inorganic phosphate of the plasma, as determined in health under the above conditions, is accepted as being 5 mg. per 100 c.c.—an upper limit which probably errs in being on the high side—definite phosphate retention was present in 33 out of 142 observations: 19 patients of the 73 examined showed a phosphorus content above this level. Of these in 8 the phosphorus exceeded 10 mg., in 4 it lay between 6 and 8 mg., while in the remaining 7 the phosphorus level was below 6 mg. but above 5.

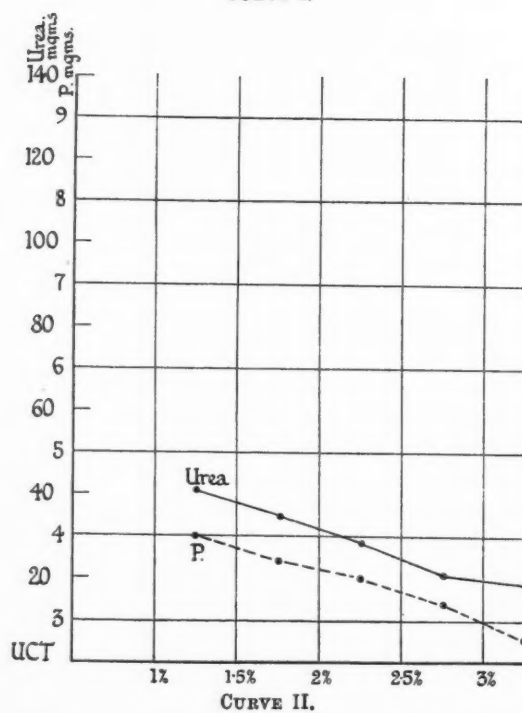
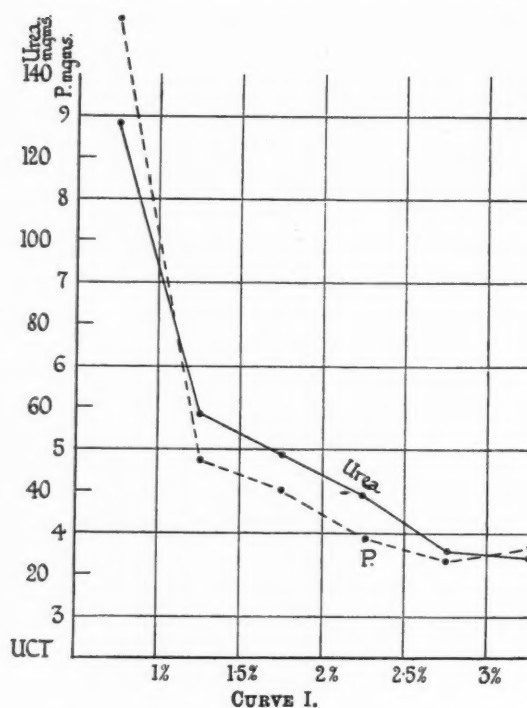
Of the 8 cases which showed a rise in the inorganic phosphorus content of the plasma to a figure above 10 mg. all are dead. This group includes 3 cases of chronic interstitial nephritis, 2 diffuse subacute nephritis, 1 acute nephritis, 1 amyloid disease, and 1 pyelo-nephritis. The prognostic significance of marked phosphate retention is therefore exceedingly bad.

The next question that arises is that of the type of renal functional failure which is associated with retention of phosphates. It will be remembered that Greenwald states that in the majority of patients phosphates and nitrogenous retention are associated, but that this is by no means invariably the case. Independent variations in the retention of the two bodies have also been noticed by the other authors who have studied the question, and have been fairly frequent in my own experience. In discussing any question of retention,

however, it must be recognized that the degree of accumulation of any substance in the blood is not only dependent on the extent to which its excretion is impaired, but also on the supply of the particular substance either in the diet or from tissue katabolism. That the supply of nitrogen and phosphorus in the diet may vary independently is well recognized. Thus Sherman (13), in a study of 150 freely chosen American dietaries, found that 41 per cent. fell short of his phosphorus standard, while in only 8 per cent. did the protein fall short of standard requirements. Again, in such conditions as growth and pregnancy, the demand for nitrogen and phosphorus for new tissue construction, a demand which is at times very considerable, will not necessarily correspond. Lastly, there is some evidence that variations may from time to time occur in the distribution of waste bodies between the blood and tissues. In a recent paper, Rohonyi and Lax (14) record large retentions of nitrogen in renal disease without alteration in the non-protein nitrogen of the blood, and give reasons for supposing that the excess of nitrogen was not necessarily stored as protein. They suggest that in the last stages of nephritis the tissues lose their 'nitrogen affinity', and that a rapid rise in the non-protein nitrogen of the blood results. It is certainly not uncommon to see such a rapid 'premortal' rise in the non-protein nitrogen of the blood in patients suffering from nephritis, in whom, owing to continuous vomiting, the ingestion of food is almost negligible.

To eliminate such sources of variation as far as possible a series of 61 observations on 36 cases of nephritis have been averaged, and the following curve plotted (Curve I). The abscissae represent the results of the urea concentration test, the ordinates the average of the corresponding urea and phosphorus contents of the blood. Cases showing a blood urea above 200 mg. have been excluded, since the corresponding urinary urea concentration would give far too favourable a picture of the actual renal efficiency when compared with the results of the urea concentration test in cases showing a less degree of damage. A few observations on cases of acute nephritis, with a rapidly falling blood urea, are also excluded. In such cases rapid changes in the renal efficiency may be taking place, and a raised blood urea may merely represent the residuum of an accumulation that has occurred during the height of the disease. Such accumulations are also favoured in acute nephritis by the oliguria which is so frequently present, and may occur even when the concentrating power of the kidney for urea is relatively satisfactory. The condition, in fact, resembles to some extent that seen in connexion with cardiac disease, or in the oliguria resulting from excessive vomiting, in which, in spite of excellent renal function and high urea concentrations in the urine, accumulation of urea in the blood results, owing to the fact that the amount of water excreted is too small to carry away the daily quota of urea, even when concentrated to the maximum of which the kidney is capable.

It is at once obvious that, if one averages a series of albuminuric cases, the blood urea and inorganic phosphorus contents run a parallel course: although in individual cases independent variations in the retention of the two substances may occur, the excretory mechanism for both bodies is in all probability the



same. The dissociation of retention of inorganic phosphorus and of urea that is not infrequently observed would appear to depend on extraneous circumstances, such as dietetic differences, rather than on the existence of two specialized excretory mechanisms in the kidney. It would, in fact, be possible in an averaged series of cases to predict the degree of phosphate retention from the results obtained by the urea concentration test. In addition, the curve appears to afford good evidence of the value of the urea concentration test in estimating renal efficiency. Even with the lesser degrees of impairment of renal function, as estimated by this test, the blood urea shows a definite tendency to rise.

To show the effect of extraneous circumstances on the degree of accumulation of the two bodies in the blood, Curve II is given, constructed on the same lines from cases of albuminuria in pregnancy (21 cases, 32 observations). The blood picture under these conditions shows very definite differences. The curve is on an altogether lower level, and the tendency to accumulation in the blood with the corresponding grades of renal damage, as estimated by the urea concentration test, is less marked. This is more especially noticeable in the case of the inorganic phosphates. In normal pregnancy the blood content in phosphorus and urea tends to be low (15), presumably owing to the demand for nitrogen and phosphorus for the purposes of new tissue construction, and renal damage in pregnancy is therefore less likely to lead to gross accumulations. Even though, in the course of pregnancy, substances are apparently produced which tend to damage the kidney, the actual work which the organ is called upon to perform is diminished, since, as the result of new tissue construction, the amount of waste substances needing excretion is less than in the non-pregnant condition. The renal lesions of pregnancy can hardly be attributed to the overstraining of a normal function.

Lastly, though in some acute cases moderate degrees of phosphate retention clear up, the higher grades of phosphate retention appear generally to be progressive. The one exception noted in this series was Case 7, in which the plasma phosphorus, which had reached a very high level, fell to a considerably lower figure, in association with other evidence of functional improvement. The improvement was, however, rapidly followed by a relapse and death in uraemia. Unfortunately, owing to the presence of gross oedema, it was impossible, during the last stage of the illness, to obtain blood for further examination.

The Serum Calcium.

The normal serum calcium content is generally believed to lie between 9 and 11 mg. per 100 c.c. of serum. In the present series a considerable proportion of the cases investigated showed abnormally low figures, but no such diminution was found as that reported by Marriott and Howland. These authors, working by another method, found in some of their nephritic patients a serum calcium as low as 1 mg. per 100 c.c. My own figures agree more closely with those given for a few cases of nephritis by Halverson, Mohler, and Bergheim.

In acute nephritis a reduction of the calcium to a figure below 9 mg. was not uncommon, a return to a normal figure accompanying recovery. In 11 of 142 observations a calcium content below 7 mg. was found, the lowest figure noted being 5.1 mg. Five of 6 cases in which these very low calcium levels occurred terminated fatally.

No completely satisfactory explanation of the fall in the calcium in nephritic sera has as yet been given. Binger (16), in a study of the effect of injections of phosphoric acid and its salts in the dog, found that such injections led to a fall in the level of the serum calcium to the neighbourhood of 6 mg. per 100 c.c. In two experiments, phosphate injections produced a fall in the serum calcium to a similar level in nephrectomized and eviscerated dogs. The disappearance of calcium from the blood was not therefore due to increased elimination through the usual channels, but was presumably the result of direct precipitation of the calcium by the excess of phosphate present.

Tisdall (17), in a recent paper, notes a similar diminution in the calcium of the serum as the result of injections of dibasic sodium phosphate and of phosphoric acid. Greenwald (18), in criticism of Binger's results, suggests that the fall in calcium observed was merely a dilution effect, resulting from the large bulk of fluid injected, and from a re-calculation of Binger's figures concludes that this is in fact the case. He was able in his own experiments, by large injections of such salts as sodium chloride or sodium sulphate, preceded by considerable bleedings, to produce a fall in the serum calcium similar in extent to that which followed injections of phosphates.

This possibility of a reduction in the serum calcium content as the result of dilution has to be taken into account in a consideration of the low calcium contents frequently encountered in nephritis. It has also to be recognized that a considerable fraction of the serum calcium (about one-third) is present in a colloidal form, combined with the proteins of the serum, and that the serum protein is frequently reduced in nephritis, especially in the hydraemic form in which marked dilution of the blood is present. Such a reduction presumably tends to lower the calcium fraction which is normally present in colloidal combination, and might to a certain extent account for the low calcium content of nephritic sera. An inspection of the tables shows a certain rough correspondence between the percentage of serum solids and the calcium content, and suggests that blood dilution may be a factor in the fall in the serum calcium. The patients whose serum solids are at a normal level (9-10 per cent.), and whose blood is therefore probably not appreciably diluted, usually show a normal calcium content, and vice versa. Such glaring exceptions to this rule are met with, however, that it is obvious that dilution cannot be the sole factor concerned. In such a case as No. 9, whose serum calcium was the lowest of the whole series, no oedema was present, and the serum solids were at a normal level. The possibility that a hydraemia was actually present, but was masked by the accumulation of waste products in the blood, appears to be excluded by the fact that the serum protein content, estimated on two occasions, was found to amount to 7.4 and 7.5 per cent., which

may be regarded as a normal figure. Further, though, in short physiological experiments, mobilization of calcium may fail to keep pace with the rapid changes of blood volume produced, there is no doubt that a considerable store of available calcium is present in the organism, which could be utilized in the comparatively slow changes of blood volume occurring in disease. In the case referred to, calcium lactate in large doses was administered by mouth throughout the period of the observations, but did not prevent a steady fall in the serum calcium, which would suggest that the low calcium observed was not due to a lack of available calcium, but rather to a change in the chemical composition of the blood interfering with the holding of the element in solution.

Such a change in blood composition may possibly be found in the presence of excessive amounts of phosphate in the blood. Just as in rickets a diminution of the serum phosphate is associated with defective deposition of lime salts, so with excessive amounts of phosphates present calcium tends to precipitate out. To test this point 69 observations on nephritis were averaged, with the following results:

Plasma P, Inorganic.	Serum Calcium.
2-4 mg. per 100 c.c. (23)	9.7
4-5 " " (23)	9.43
5-10 " " (10)	8.3
10 upwards (13)	6.6

There would seem, therefore, to be an inverse relationship between the amount of inorganic phosphorus present and the calcium content of the serum: and it appears probable that the low calcium content of the serum of many cases of nephritis may be attributed in part at least to the presence of a phosphate retention, with, as a possible contributory factor in the hydraemic cases, a diminution in the protein content of the serum.

In the preceding remarks no reference has been made to one remarkable case which showed a calcium content approximately double that normally found (Case 20). This patient has been excluded from the averages given above on account of the altogether exceptional nature of the blood picture, and because the diagnosis remains in some doubt. In a series of calcium estimations in more than 150 cases, no serum calcium content above 10.8 mg. per 100 c.c. has been encountered; in this patient the serum calcium at one time amounted to 20.1 mg. The history of the case was briefly as follows: In 1916 he had suffered from attacks of vomiting, which lasted for three months. In June 1922 the vomiting recurred; it was accompanied by nausea but not by pain, and was not much influenced by diet. A considerable degree of wasting had resulted. On examination no abnormal physical signs were present; the blood-pressure was 155; no retinitis was present. The urine showed a trace of protein and occasional hyaline and hyalo-granular casts. No headaches were complained of. The electrical reactions were normal. From the date of admission until December 1 the patient vomited once or twice daily; after this date the vomiting ceased almost completely, and at the time of the last observation the patient had not

vomited for six weeks. The blood examinations showed a marked urea retention, without any accumulation of phosphates. The urinary urea concentration was very poor, and a high grade of damage to the nitrogenous excretory function of the kidney, with a definite polyuria, was undoubtedly present. A test meal showed a normal gastric acidity. The last blood examinations showed a considerable fall in the urea retention, and the patient appeared to be improving. Attempts to lower the serum calcium by bicarbonate administration (22.11.22-28.11.22) and by doses of di-sodium phosphate (15.12.22-11.1.23) produced no definite effect.

It is suggested that these findings may be connected with the parathyroid hyperplasia, which has been described in chronic nephritis, and the case appears to be worth recording, since, as far as I am aware, no serum calcium content approaching this figure is to be found in the recent literature, with the exception of certain determinations on cows by Hart and his collaborators (19). Allers and Bondi (20) also were able to double the calcium content of the blood in rabbits by feeding large doses of hydrochloric acid. In this patient there were, however, no symptoms suggesting an acidosis, and the maintenance of the urine at an alkaline reaction for six days by means of sodium bicarbonate failed to influence the condition.

Hydraemia.

The question of hydraemia may be dealt with very briefly. The lowest observed figure for the total solids of the serum was 5.4 per cent., the highest 10.4. It appears probable, from the rapid changes in the percentage of solids that may occur, and from the association of low figures with generalized oedema, that such reductions in the serum solids are the result of dilution of the blood rather than of an actual diminution in the amount of protein and other substances in the vessels. The dilution of the blood in the higher grades of oedema would, therefore, be equivalent to about 80 per cent.

The solids of the serum are of course mainly composed of protein; and it is interesting to observe that, if we may judge from the percentage of solids present, there is no definite tendency to restoration of the protein content of the blood to a normal percentage in cases in which long-continued oedema is present. Thus, in a case of nephritis complicated by pregnancy, which was followed for five months, the slight variations in the solids observed accompanied corresponding changes in the oedema, and there was apparently no attempt to restore the serum protein to a normal level. Apart from this, the percentage of solids present in the serum shows few features of interest, and has only been estimated in order to afford some indication of the degree of hydraemia present.

Uraemia.

As has been mentioned at the commencement of this paper, it is still doubtful whether we can correlate any of the phenomena of uraemia with retention of nitrogenous waste products. It is well known that one patient may exhibit

severe symptoms with a blood urea of 150 mg. per 100 c.c., while another, with a similar degree of urea retention, may be in relatively good health, and it is also known that death occurs at very different levels of nitrogenous retention. Again, the prognosis of a case of nephritis from a single examination of the blood urea is often difficult, since clinical recovery may be seen even in cases in which the blood urea content has reached such a figure as 250 mg. per 100 c.c. The question therefore arises whether the estimation of any other normal blood constituent will yield us more valuable information as to the condition of the patient and the ultimate prognosis, and whether, if such a constituent exists, its accumulation shows a more direct connexion with the symptoms of the disease.

It is unfortunately extremely difficult to define the essential symptoms of uraemia. In cases in which we encounter complete abolition of the urinary excretion, such as bilateral calculus suppression, or the removal of the only functioning kidney, symptoms are on the whole remarkable for their absence, and the cause of death may be obscure, as it is in certain liver lesions. Convulsions, for instance, occur in a small proportion only of such cases. A very similar condition is not infrequently seen in such cases of chronic fibrotic disease of the kidney as No. 9. In this patient, the only symptoms noted had been attacks of vomiting of four months' duration. He had never suffered from headache, and only sought medical advice twelve days before his death. Examined immediately after admission, he showed the grossest urea retention of the series, and died within a fortnight without further symptoms, except vomiting, muscular twitchings, increasing drowsiness, and ultimately cardiac failure. Extreme degrees of renal functional failure need not therefore be associated with any especially dramatic happenings; on the contrary, it is in these extreme cases of nitrogenous retention that the diagnosis may be first established by a chemical examination of the blood, the patients often having been admitted for gastro-intestinal symptoms. Such gastro-intestinal symptoms are possibly the most characteristic feature of the uraemic state.

It has already been pointed out that phosphate retention, if marked, is of extremely grave prognostic import. This fact appears to be capable of two interpretations. In the first place, it is possible that a rise in the inorganic phosphorus of the plasma is merely an indication of a grave degree of renal failure. On this assumption a high phosphate content would correspond in significance to a rise in the creatinin. As is well known, accumulation of creatinin in the blood of a patient suffering from nephritis is suggestive of a fatal termination, not presumably owing to any toxic action of creatinin *per se*, but because creatinin does not accumulate in the blood unless very severe renal damage is present. Mayrs (23) has recently shown that the concentrating power of the kidney for phosphate and creatinin is approximately the same, while urea is concentrated to a slightly less degree. On these lines, accumulation of either creatinin or phosphate in the blood would merely indicate that the damage to renal function was extreme.

Phosphate Retention.

The other possible explanation of the bad prognosis involved in phosphate retention is that the phosphate is in itself toxic. This question of the toxicity of phosphates has been mainly studied from the point of view of the production of tetany by phosphate injections. Binger has been able to produce very definite symptoms in dogs by injection of di-sodium phosphates; vomiting, diarrhoea, fibrillary twitching, and tetany resulted. Tisdall, in a recent paper, records similar results. Of four dogs which received dibasic sodium phosphate injections three died. In both series of experiments the toxic dose amounted to about 150 mg. of phosphorus per kilo, an ultimate concentration approximating to that found in severe cases of nephritis in man. Both observers find that a marked fall in the serum calcium follows the injection. The interpretation of these results is, however, obscured by the fact that equivalent injections of orthophosphoric acid, though followed by the same fall in the serum calcium, produce no ill effects. Greenwald (18) and Tisdall (17) conclude that the symptoms produced by di-sodium phosphate injections are the result of a disturbance in the calcium-sodium ratio of the serum rather than of a directly toxic action of the phosphate, and the former worker has shown that similar results may be produced by injections of other sodium salts. Tisdall, in his study of the serum after phosphate and phosphoric acid injections, has shown that a slight fall in the total sodium occurs after injection of orthophosphoric acids, but the difference, shown in his table, between the calcium-sodium ratio after di-sodium phosphate injections and after injections of orthophosphoric acid is comparatively slight. The blood picture produced by the acid injection is, however, more suggestive of that found in human nephritis, in that the CO_2 combining power of the plasma is diminished, and the P_H tends to the acid side. It may be objected to these experiments that the bleedings and injections are very large, that the kidneys remain intact, and that the period of observation is comparatively short.

If, however, we turn from the results of experimental procedure to the findings in disease, an increase in the inorganic phosphorus of the plasma appears to be closely associated with the development of the symptoms of uraemia. In the present series ten fatal cases have been encountered. Of these one (No. 8), a case of parenchymatous nephritis, without phosphate retention, died from an intercurrent primary peritonitis. Another (No. 30), a patient suffering from nephritis complicated by pregnancy, died after induction, with evidence of gross impairment of nitrogenous excretion, and with marked urea accumulation in the blood, but without any appreciable increase in the plasma phosphate. The post-mortem examination showed, in addition to the renal lesion, extensive pyaemic abscesses of the liver, and death appeared to have been due to sepsis rather than to uraemia.

In the remaining eight cases death resulted from uraemia, and in all gross phosphate retention was present. An increase in the plasma phosphate appears,

therefore, as far as this series is concerned, to be the rule in patients dying from uraemia.

On the other hand, cases occur in which great impairment of excretion of nitrogenous waste products is present, with large accumulations of urea in the blood, in which the plasma phosphate content is only slightly raised. As instances of this condition, two cases of renal infantilism may be cited, for the opportunity of examining which I am indebted to Dr. C. R. Box (Nos. 11, 12). In these patients, as will be seen from the table, gross defects of nitrogenous excretion were found, with resultant high blood urea contents; the phosphate content of the plasma was, however, only slightly raised. Both children, though anaemic, stunted, and far from robust, showed no definite symptoms of uraemia and were able to attend a special school. It is possible that the relatively low phosphate content in the blood of such cases may be associated with the demand for phosphorus for purposes of bony growth. In contrast to this condition of affairs, a case of amyloid disease (No. 13) with a similar grade of urea retention, but with a plasma inorganic phosphorus content of 14.2 mg. per 100 c.c., was suffering from attacks of nausea, vomiting, and dizziness at the time of the estimations, and died three days later. Case 6, again, with a blood urea content of 48 mg. only, but with a definitely increased plasma phosphorus, showed definite uraemic symptoms. Lastly, in Case 7, during the period covered by the first two observations the patient was acutely uraemic (vomiting, drowsiness, and frequent fits), while at the time of the last observation a very marked clinical improvement had occurred, and the patient was perfectly conscious, free from symptoms, and eating well. This improvement coincided with a very marked drop in the plasma phosphorus, while the blood urea remained at a higher level than at the commencement of the uraemic period.

It would appear, therefore, that the symptoms which we associate with uraemia are more closely connected with phosphate than with nitrogenous retention. The exact significance of this phosphate retention remains, however, doubtful. We may, on the one hand, regard the phosphate retention as merely symptomatic of very severely impaired renal function. In this case we are faced with the difficulty that if we take patients in whom, as estimated by the urea concentration test, or by the degree of urea retention present, the degree of functional failure is the same, the occurrence of symptoms and the ultimate issue appear to depend largely on the presence or absence of phosphate retention. As has been shown above, the same excretory mechanism appears to be concerned in the diminution of both urea and phosphate, and independent variations in the accumulation of the two bodies are probably conditioned by extraneous circumstances. On the other hand, though the clinical evidence appears to be in favour of the toxicity of the phosphate ion *per se*, the experimental findings are, on the whole, against such an assumption. In human nephritis the blood picture corresponds in all probability to that found after injections of orthophosphoric acid. We have the same tendency to a change in the reaction of the blood, and the same diminution in the bicarbonate content of the plasma, with the resulting

hyperpnoea which is so commonly observed in uraemia. Injections of ortho-phosphoric acid are, however, not productive of symptoms. Though experimental evidence would suggest that the phosphate is neither directly nor indirectly responsible for the symptoms, it must be recognized that under experimental conditions the kidneys are intact, excretion of phosphates is continuing, and the tendency is towards a rapid return to a normal condition. In nephritis, on the other hand, no such healthy condition of the kidneys is present, and it is possible that the long-continued exposure of the tissues to the deleterious influence is the cause of the symptoms observed. In any case, there can be no doubt that from a clinical standpoint retention of phosphates is definitely associated with the occurrence of the symptoms of uraemia, and that, from the point of view of prognosis, a study of the phosphate content of the blood is of the greatest value.

The Calcium Content of Serum.

In view of the work of Loeb, who has shown the effect of a diminution of the calcium content of solutions in increasing the excitability of nerve, a connexion might be expected between the diminished calcium content of the serum in nephritis and the occurrence of convulsive phenomena. In the present series of cases convulsions have occurred in four cases only—one a case of subacute diffuse nephritis, the remainder cases of eclampsia. The latter type of case may reasonably be included in any discussion of nephritic convulsions, since at present we have no means of differentiating eclamptic from so-called uraemic fits except by the co-existence of a pregnancy. In none of these cases was any marked fall in the calcium of the serum present; the lowest figure noted was 7.8 mg. per 100 c.c., while in one eclamptic the calcium stood at 8.4 mg. and in the nephritic at 8.5 at a time when convulsions were actually occurring. Since in numerous cases the calcium fell to a considerably lower level and no convulsions ensued, there appears to be no reason to suppose that the cause of the convulsions lay in a deficiency of serum calcium. Neither, if we may draw conclusions from eclamptic fits, is the cause to be found in any accumulation of the various waste products that have so far been studied. Speaking generally, the convulsions of renal disease appear to bear a closer relationship to an increase of blood-pressure and to the presence of hydraemia than to any other known factors. As is well recognized, a rise in blood-pressure, usually accompanied by headache, is often the prelude to the convulsions of eclampsia, and a similar sequence was frequently observed in patients suffering from so-called trench nephritis in France. Whether the connexion between a raised blood-pressure and convulsions is one of cause and effect, or whether some as yet undetermined body produces both the blood-pressure rise and the convulsions, is at present unknown.

Apart from generalized convulsions, there are certain other nervous phenomena associated with uraemia which may not improbably be related to the diminished

content of the serum in calcium. These are the localized twitchings and general tremor which, though less striking symptoms than actual generalized convulsions, are certainly of worse prognostic import. In the material under discussion these symptoms were present in three patients, all of whom died. In all three the calcium of the serum had fallen to a lower figure than 7 mg. per 100 c.c., and in the patient who showed these symptoms in their most marked form the calcium content was the lowest of the series (Case 9). It is noticeable that in such cases the calcium may fall to a level at which symptoms of tetany might be expected to appear. Actually no such symptoms are found, nor are Trousseau's or Chvostek's signs present. The appearance of tetany is not, however, solely conditioned by the total amount of calcium present, but is also determined by the extent to which the element is ionized, and probably by alterations in the ratio between the calcium and the other inorganic ions of the blood. The most important factor in this latter ratio appears to be the balance between divalent (Ca, Mg) and monovalent ions (K, Na), and there is evidence that any reduction in the proportion of divalent ions tends to produce symptoms of tetany. In the condition known as gastric tetany, however, there is no diminution in the amount of divalent ions present, and the most significant change in the blood is the marked increase in the bicarbonate ion (17). This increase probably produces a diminution in the active ionized fraction of the calcium, and tetany results even with a normal serum content of this element. In nephritis, on the other hand, there is usually in the severer cases a diminution in the bicarbonate content of the plasma, which, with the tendency to a rise in the hydrogen ion concentration of the blood, will favour the ionization of the diminished amount of calcium present, and militate against the appearance of symptoms of tetany.

Lastly, the question of the relationship between renal damage and a raised blood-pressure may be briefly touched on. Though a raised blood-pressure is typically associated with the azotaemic type of renal function failure, there can be no doubt that this connexion is to some extent inconstant. In Cases 9 and 27, for instance, with very marked degrees of this type of renal functional failure, no rise in blood-pressure was present. It is also a common experience to find patients with greatly raised blood-pressures, in whom no evidence of impairment of nitrogenous excretion can be obtained. A typical instance of this condition is seen in Case 25; in this patient a greatly increased systolic pressure, which was at first regarded as evidence of the presence of a toxæmia of pregnancy, persisted after delivery, but the renal function throughout was perfectly normal. In such cases we apparently have to deal with a primary hyperpyrexia, independent of any functional damage to the kidney.

In acute cases with oedema a certain parallelism is observed between the rise of blood-pressure and the degree of blood dilution (hydraemia plethora), and the concentration of the blood which accompanies the disappearance of the oedema is followed by a fall in the blood-pressure (21). In artificially induced hydraemic plethora, such as occurs after injections of sugar solutions, a definite rise in blood-pressure is found (22), and we are probably justified in assuming

that some of the transitory increases in the blood-pressure observed in cases of nephritis are due to this cause. In parenchymatous nephritis, however, in which long-continued and marked hydraemia is present, the blood-pressure is usually at a normal level (Case 8). In the majority of cases of renal disease we have to admit that we can assign no cause for the increased blood-pressure that is so frequently found. Though it is probably due to vascular changes, the factor producing these changes is still unrecognized, and does not appear to be any of those substances whose retention and excretion in nephritis has as yet been investigated.

Treatment.

As regards treatment, it is worth considering whether the examination of the inorganic constituents of the blood gives us any ground for a rational therapy. In the first place, it is exceedingly doubtful whether we at present have any means at our disposal of permanently raising the calcium content of the blood, or even restoring it to a normal level. The effect of intravenous injections is purely transitory, and most observers have failed to find any rise in the blood calcium after ingestion of calcium salts. The results of administration of calcium by the mouth in acute nephritis, as reported by Halverson, Mohler, and Bergheim, are probably due to natural recovery, as they themselves suggest, rather than the effect of the treatment employed. Similar increases in the serum calcium were seen in Cases 1, 2, and 3 of this series without any calcium medication, and in Case 9, to which calcium lactate was administered in large doses, absolutely no effect was observed.

Apart from any action in raising the calcium content of the serum, oral administration of calcium may act indirectly in preventing absorption of phosphorus. Telfer (6) has recently confirmed the work of previous investigators, who found that the addition of calcium salts to the diet greatly reduced the absorption of phosphorus and might render the urine phosphate free. On these grounds, if we believe that accumulation of phosphates in the blood is in any way the cause of the symptoms of uraemia, large doses of calcium by the mouth would be indicated in the treatment of this condition. The results of clinical experience are of some interest in this connexion. There is a general consensus of opinion that meat, which contains a high percentage of phosphorus and a low calcium content for its caloric value, should be avoided in nephritis; milk, on the other hand, which has a considerable reputation in the treatment of nephritis, though it contains a fair percentage of phosphorus, is singularly rich in calcium. Both substances are, of course, rich in nitrogen, but no evidence of the toxicity of the nitrogenous metabolites has as yet been produced, and, apart from the general principle of sparing a damaged function, there does not appear to be any reason for specially avoiding the ingestion of nitrogenous food-stuffs.

Conclusions.

1. A marked increase of the phosphate content of the blood in nephritis is of extremely grave prognostic import.

2. The symptoms of uraemia appear to show a close relationship to phosphate retention.

3. On the average, retentions of phosphates and urea run a parallel course: the excretory mechanism for the two bodies is probably therefore the same. Independent variations in the retention of the two bodies are frequently observed, and are probably due to circumstances extraneous to the renal function.

4. A diminished content of serum calcium is a bad omen, and appears to be connected with the generalized tremor and local twitchings of the final stages of uraemia. No connexion has been found between a diminution in the serum calcium and the generalized convulsions.

5. The calcium content of the serum in nephritis appears to show an inverse relationship to the content of inorganic phosphorus.

6. The effects of pregnancy on retention are shown.

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TABLE I. *Acute Nephritis (mixed type).*

Case No.	Age.	Sex.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.
1	9	♂	9.2.22	7.6	9.4	97	8.2	(0.95)	115
			15.3.22	4.9	9.9	34	9.5	1.65	105
			3.4.22	4.3	9.6	30	8.9	1.8	104
			14.9.22	4.1	10.6	18	9.1	2.3	98
2	36	♂	25.4.22	4.0	8.9	68	6.9	1.8	180
			5.5.22	3.6	9.5	30	7.9	2.1	117
3	9	♂	10.3.22	6.7	8.7	164	8.1	(1.7)	94
			7.4.22	4.0	10.8	33	9.4	2.7	96
(Azotaemic type—no oedema at any time.)									
4	16	♂	13.9.22	4.1	10.3	96	9.5	2.2	96
			21.9.22	4.4	10.6	37	9.5	2.0	100
			11.10.22	3.6	10.3	21	9.2	2.7	110

TABLE II. *Sub-acute Nephritis (mixed type).*

Case No.	Age.	Sex.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.
5	9	♀	21.4.22	3.4	8.6	30	8.6	2.4	95
			8.5.22	4.5	9.1	35	6.0	1.7	110
			1.6.22	5.0	8.7	28	6.7	1.9	110
			9.8.22	3.2	9.0	26	8.0	3.1	112
6	19	♀	14.8.22	8.9	6.9	48	5.9	1.0	190
			23.8.22	12.0	7.2	88	6.5	(0.65)	170
			28.8.22	12.4	6.9	100	6.7	(0.55)	175
			26.9.22	13.2	6.8	106	6.6	(0.70)	170
			14.11.22	15.1	6.1	171	7.0	—	175
			Died 20.11.22 (uraemia).						
7	27	♂	12.4.22	19.0	8.5	182	7.4	(1.60)	210
			21.4.22	21.4	9.1	330	8.5	(0.75)	190
			25.5.22	7.7	8.4	261	7.5	(1.15)	160
			Died 21.6.22 (uraemia).						
8	8	♂	Sub-acute nephritis (hydraemic type).						
			17.8.22	5.1	7.8	31	5.8	3.2	100
			29.8.22	4.3	7.5	22	6.2	4.5	95
			13.9.22	4.4	8.0	35	6.6	3.8	98
			Died 10.10.22 (peritonitis).						

TABLE III. *Chronic Nephritis (Azotaemic type).*

Case No.	Age.	Sex.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.
9	46	♂	12.6.22	12.9	5.8	546	9.8	(1.1)	130
			15.6.22	14.0	5.2	531	10.3	(1.0)	134
			19.6.22	18.2	5.1	561	9.5	(1.1)	124
			Died 23.6.22 (uraemia).						
10	44	♂	27.10.22	15.5	6.9	492	8.5	(0.71)	210
			Died 25.10.22 (uraemia).						
11	7½	♀	4.5.22	5.0	10.1	162	8.9	(0.6)	100
			6.8.22	4.7	9.4	122	8.9	(0.5)	102
12	10	♂	28.4.22	6.4	9.6	112	9.3	(0.7)	110
			20.9.22	6.1	8.9	196	8.6	(0.65)	102
13	28	♂	Chronic nephritis (amyloid disease).						
			31.7.22	14.2	6.5	198	8.9	0.95	120
			Died 4.8.22.						
			Albuminuria with casts (no symptoms).						
14	55	♂		3.1	10.6	27	9.9	2.7	155
15	19	♀		2.9	9.8	17	8.8	1.9	120*
16	56	♀		2.9	10.6	23	9.6	2.6	132
17	18	♂		3.8	9.4	23	8.9	2.8	105
18	28	♂		3.2	9.9	34	9.3	2.3	112
19	57	♂		3.2	9.8	37	9.1	2.7	130

* An excised portion of the kidney showed definite evidence of interstitial nephritis.

TABLE IV. *Chronic Nephritis—Azotaemic type (anomalous).*

Case No.	Age.	Sex.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.
20	37	♂	13.11.22	4.8	20.1	125	10.4	(1.5)	155
			20.11.22	5.1	18.5	132	10.2	(1.3)	155
			27.11.22	4.6	16.2	126	9.4	(0.7)	160
			13.12.22	3.4	17.1	146	8.6	(1.2)	104
			21.12.22	3.4	18.3	150	8.7	(1.2)	100
			1.1.23	3.4	15.6	70	8.3	1.1	125
			11.1.23	3.3	13.8	48	8.5	1.1	125

TABLE V. *Toxaemias of Pregnancy.*

(a) Mild type.									
Case No.	Age.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.	
21	32	29.9.22	2.7	9.5	14	9.3	3.1	132	Delivered 12.10.22.
		23.10.22	3.8	9.5	22	8.2	4.3	108	
22	30	26.10.22	3.7	9.2	27	8.0	2.3	145	Delivered 31.10.22.
		7.11.22	3.6	9.4	27	8.3	2.7	112	
(b) Severe type.									
23	24	15.5.22	4.9	10.1	42	8.9	2.1	183	Child dead : induced.
		18.5.22	3.9	10.1	29	8.9	2.2	156	
		25.5.22	3.1	9.7	23	8.5	2.3	130	
		23.11.22	3.3	—	19	—	2.8	122	
(c) Eclampsia.									
24	25	6.10.22	3.8	9.4	30	7.1	2.9	182	During fits.
		9.10.22	4.5	8.4	58	7.4	—	—	
		20.10.22	3.6	9.5	20	9.2	2.9	120	
		4.12.22	3.6	10.1	23	9.9	2.9	114	
Pregnancy and hyperpyresis.									
25	35	11.10.22	2.8	10.0	16	9.7	3.5	204	Delivered 5.11.22.
		20.10.22	3.0	9.8	20	9.7	3.4	202	
		6.11.22	3.2	10.0	23	9.5	3.6	185	
		21.11.22	—	—	—	—	—	185	

TABLE VI. *Nephritis complicated by Pregnancy.*

Case No.	Age.	Date.	P.	Ca.	Urea.	Solids.	U.C.T.	B.P.	
26	34	8.8.22	3.6	9.5	58	9.4	1.4	132	Delivered 27.9.22.
		8.9.22	3.4	10.3	60	9.7	1.4	138	
		4.10.22	3.8	9.8	69	7.3	1.5	132	
		3.11.22	7.5	8.1	91	6.4	(0.8)	98	
		29.11.22	17.5	6.6	269	7.7	(0.7)	118	
Died 2.12.22 (uraemia).									
27	26	23.1.22	3.3	8.6	30	8.4	1.2	140	Induced 28.4.22.
		17.2.22	3.3	9.3	38	8.6	1.3	150	
		8.3.22	3.7	9.2	42	8.7	1.3	146	
		23.3.22	3.2	9.2	38	8.9	1.7	142	
		24.4.22	2.9	9.1	35	8.6	1.6	144	
		9.5.22	3.5	10.2	45	8.4	2.4	135	
		7.12.22	3.8	—	28	—	2.0	108	

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A COMPARATIVE STUDY OF BASAL METABOLISM IN NORMAL MEN¹

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General.

IN every branch of medicine of the present day the endeavour is very obviously being made to break away from the purely anatomical study of disease and to seek for functional tests which give a measure of the degree of pathological disturbance of the individual as compared with the normal. Moreover, it is only by following such paths that the science of medicine can progress and stand in equal state with the exact sciences. Lewis's work upon the heart, Dreyer's work upon physical measurements, and Ambard and Maclean's work upon the kidney may be cited as instances.

The study of the metabolic rate of individuals suffering disturbances of the thyroid gland has opened up an entirely new field of investigation into the character and degree of these disturbances and the efficacy of the remedial measures at present employed. In many other conditions the study of the metabolic rate gives promise of valuable assistance in diagnosis, prognosis, and treatment.

In this, as in all functional tests, the establishing of an accurate normal base line is of fundamental importance before it is possible to interpret the results obtained by examination of persons who are, or may be, suffering from a pathological disturbance.

The difficulty of establishing a base line for metabolism has become more apparent as each investigator of the subject has undertaken its close study. While there is fairly general agreement upon the character of the fundamental factors which influence metabolism among those who have examined considerable numbers of individuals, there is disagreement as to the relative importance of these fundamental factors and the methods to be employed for determining the normal in any given instance.

A critical survey of the history of the subject is beyond the scope of the present paper, but a brief summary of the position is necessary.

Three methods of calculating the normal basal metabolic rate have been

¹ Report to the Medical Research Council.

advanced, with the backing of a considerable body of experimental evidence. No series of observations hitherto published has contained all the data necessary for an accurate comparison of the methods. All three methods agree upon the fundamental influences of sex, age, and body size, but show considerable differences in their method of treating the last factor—body size.

1. Benedict (1) and his co-workers have declared against the 'surface law' originally advanced by the earlier French investigators, and by Rubner in Germany, and they have worked out relationships between metabolism, sex, age, weight, and standing height. If weight alone, or standing height alone, be taken as the measure of body size, the relationship with metabolism is less close than when both factors are considered.

2. Du Bois (2) adheres to the 'Body Surface' Law, and has worked out an improvement upon Meeh's method for determining the surface area of the body, by taking into account both weight and standing height. Age and sex are adjusted by an appropriate series of caloric values per square metre of surface in making the calculation for the normal metabolism.

3. Dreyer (3), in a preliminary communication, has published a formula derived from Benedict's series of observations upon males and females, which he has applied to the series of published observations of other investigators, where comparative experimental conditions have been secured. In his analysis of the results he shows that this formula gives a small but definite improvement between observation and calculation, as compared with the other two methods. His analysis of the available material lends no support to the Body Surface Law, and takes into consideration weight, sex, and age—but with this important difference, that he maintains that metabolism should be related to the 'normal weight' of the individual, rather than to the observed weight, which is subject to change under physiological and pathological influences. The measurements necessary to determine the 'normal weight' of the individuals of Benedict's series were not available, and the values published in his formula were derived from the observed weight; it is possible, therefore, that these values may require some slight modification.

The normal individual. It has naturally been the endeavour of all investigators of metabolism to secure for their observation normal, healthy individuals for the purpose of establishing a standard base line. The 'normal individual' would appear, from the study of text-books, to be a capricious and elusive person, liable to a metamorphosis into the 'average individual', a person of even less well-defined attributes than the 'normal individual'. The 'normal' haemoglobin standard, given by the Haldane method, gives but one striking example of how misleading such standards may be, determined by the arbitrary massing of individual observations. We now know that (i) at birth the infant possesses 150 per cent. haemoglobin as compared with its adult value; (ii) at the end of its first year it possesses only 70–80 per cent. of its adult value; and that (iii) from its first year onwards the percentage rises steadily, until it achieves its adult value about 21 years of age.

Moreover, this 'standard' entirely ignores the influence of sex, and the diurnal variations, which may show a 15-20 per cent. change in any given day.

The normality and health of an individual, therefore, is to a considerable extent dependent upon the judgement of the observer, and, in the work already carried out on metabolism, the normality of the individuals studied is open to this criticism. Benedict and Du Bois are careful to draw attention to this fact in their papers. There is no means available of forming an opinion as to the nutritional and functional normality of the individuals studied except by making comparison with the 'average' height-weight tables as a gauge of their nutritional state, and making an assumption that they were fit and normal in the eyes of their observers, as judged by ordinary clinical examination. All the observations hitherto made are lacking in greater or less degree in physical and physiological measurements which make them comparable in more than a few respects. As Benedict has shown, the 'physiological state' of an individual is one of great importance in connexion with metabolism, hence it is of value to apply very close attention to the physical quality of the individuals examined.

Benedict and Du Bois, in their series of 'normals', have each rejected certain individuals for the purpose of calculation of their standards because these individuals showed 'excessive weight' for their stature, as compared with the other individuals examined. This purely arbitrary method of selection is open to severe criticism. The true 'abnormality' of these rejected individuals is open to doubt when one considers how variable the girth of individuals of the same stature may be. Taking into consideration both length and girth, these individuals may well have been normal.

In recent years certain new methods for determining the normal weight, and examining the functional efficiency of an individual, have been developed. The methods depend upon physical and functional measurements which enable comparison to be made of one individual with another, and which are to all intents and purposes independent of the personality of the observer (4).

Special object of present work. The object of the present piece of work has been to examine a number of individuals of the male sex, covering a fairly wide range of size and age, to compare their metabolic rates, and to determine how far these conformed to each of the three best known methods of calculating the 'normal', and at the same time to examine their nutritional and functional 'normality' by tests which will enable independent observers to form some opinion as to the quality of the material examined in other respects.

Physical and functional tests other than metabolic. It is impossible to enter into any detailed discussion of the merits of these tests: the briefest description only can be given, since the details can be obtained from the original articles.

Weight. In the selection of suitable subjects what is to be the criterion of normality as regards weight?

The observed weight of an individual may or may not be his 'normal weight', and yet the physiologist wishes to examine individuals whose nutrition and general fitness are normal and good. These estimations must depend for

their value upon the uncontrolled arbitrary standards in the mind of the particular observer, or be judged by reference to the tables relating stature and weight, which have been determined from 'average' figures. Weight related to stature is a relationship between a measurement in three dimensions with one of one dimension; *ipso facto*, in human beings whose shape and configuration are highly variable, a large mean variation between prediction and observation is to be expected, and is found to occur. There are, moreover, good reasons for avoiding stature as a basic measure for comparing individuals.

Dreyer's method (4) for determining the 'normal weight' from the trunk length and chest circumference is sound in principle in that a three-dimensional measurement is related to measurements in three dimensions, and in the fact that the measures taken are measures which are constant in their relation to weight over the whole period of growth, and are not appreciably affected by disease. The enormous value of a method which enables us to determine 'normal weight' can hardly be estimated, and is an essential preliminary in any physiological system of standards in which size and weight are factors, since, with loss of weight in disease, a metabolism, vital capacity, or pulse-rate, which is entirely abnormal for the 'normal weight' (as it should be if our standards are correct), may yet be found to be normal for the reduced weight (or observed weight), or vice versa.

In this fundamental aspect, therefore, Dreyer's method of determining the normal basal metabolic rate differs from the methods of Benedict and Du Bois, who depend upon the observed weight, the normality of which is open to doubt, while Dreyer uses the 'normal weight' in his formula, which may or may not be identical with the observed weight in any individual case. When the observed weight falls within the mean error of determination of the calculated weight, it is immaterial which weight is employed for purpose of calculation.

Physical fitness. Here, again, we have no measure other than the subjective impressions of the individual examined and the estimate of the observer to guide us, and yet, for the purpose of establishing a normal base line, we wish to secure healthy individuals. Two tests of normality have been employed as controls of certain aspects of the fitness of the individuals examined in the present series, apart from a general inspection and a routine clinical examination.

Vital capacity. Dreyer (4) has shown that in the vital capacity we have a valuable functional measurement of one aspect of physical fitness, and has published tables as a guide to the estimation of the physical fitness of individuals, taking into consideration their body size and their occupation, with its associated conditions of life.

While all the individuals in the present series do not conform to the A class standard, each may be regarded as possessing a vital capacity normal for his occupation and conditions of life.

Pulse response to exercise. The simple test, as recommended by Lewis (5), has been made in each individual case, with three exceptions; the exercise

consisting of twenty rises on a chair, ten with each foot, the pulse being taken before, immediately after the exercise, and again one to two minutes after completion of the exercise. The strenuous tests have not been employed, since in every instance the subjects are in the habit of taking more or less strenuous exercise in the form of physical recreation. Lewis's test makes no claim to be applicable over any particular range of age and weight, and no absolute values can be attached to the measures taken, but it does offer an additional rough test of the functional efficiency of the cardio-vascular system of the individuals examined.

The return of the pulse-rate after exercise to the rate noted previously to the exercise, within a period of two minutes after ceasing the exercise, has been taken as normal. In several of the subjects examined the pulse had returned to the original rate within 75 seconds following the exercise, and in all cases the pulse had returned to the original rate within 135 seconds following the exercise.

Other examinations made. In each individual the following examinations were made:

(a) *Haemoglobin.* Two estimations by the technique recommended by Dreyer (6)—read in a Dubosq colorimeter against a standard glass with artificial light.

(b) *Blood-pressure.* Two determinations of the systolic and diastolic blood-pressure with a mercury manometer, using Oliver's auscultatory method; in a few cases one examination only was made.

(c) *Respiration rate and lying pulse-rate.* Four counts of each were taken during each fifteen-minute period while the subject was on the calorimeter.

Basal Metabolism.

The basal metabolic rate has been determined in all cases with the Benedict calorimeter, as supplied by the Sanborn Company. This apparatus required adjustment and modification in certain important particulars, and its management required constant attention, if reliable readings were to be secured. Details of the criticisms offered, and the remedies applied to secure accurate working, are given in Appendix I.

Certain inherent weaknesses in the method, and the use of short duration experiments, must be mentioned.

(a) It is admitted that short duration experiments must necessarily be more uncertain than long duration experiments, when the subject is examined on one occasion only, and that the psychological factor incident upon an examination of this description will hardly have time to wear off in some subjects.

(b) In all short duration experiments the CO_2 output is a somewhat unreliable guide as to the true respiratory quotient, while the O_2 consumption is not open to criticism to quite the same degree.

(c) The accuracy of the measurement of the volume of O_2 consumed depends

upon the opening and closing of the valve of the machine exactly at the end of a normal expiration, at the commencement and conclusion of the experimental period, and upon the further assumption that the depth of respiration at each time is identical. This manipulation requires considerable care, and may even so introduce an error into the reading.

The following steps were taken to control errors likely to enter into the determination for any of the above-mentioned reasons:

(a) Two fifteen-minute periods were observed in the case of each individual, with one exception (No. 51). In nearly every instance the O_2 consumption was slightly higher in the first experimental period than in the second, and if the difference between the readings exceeded 5 per cent. a third period was taken. In calculating the O_2 consumption the mean of the two readings was taken from the observations in the two comparable periods. The psychological factor appeared to be negligible in nearly all the subjects examined, with the exception possibly of one or two of the boys. In each case the procedure was carefully explained beforehand, and the boys were each given a short preliminary run.

(b) The CO_2 output was measured in the case of the adults, and the caloric value of the O_2 consumed estimated according to the respiratory quotient found, except in the case of the boys, who were inclined to become restless with the monotony of the procedures, and the delay involved in weighing the bottles. In their case, therefore, and with a few adults, a mean respiratory quotient of 0.82 was assumed in determining the caloric output.

(c) The manipulation of the valve was correct as far as could be judged in every case, though small errors may have crept in in a few cases with the boys, who were more rapid and somewhat irregular breathers, as compared with the adults.

General Conditions of the Experiments.

(a) The subjects were in each case examined in the post-absorptive state—twelve to fourteen hours after the last meal, between the hours of 9 and 11.30 a.m. (summer time).

(b) The walk or cycle ride to the laboratory in no case exceeded one and a half miles.

(c) In each case the subject was rested upon a comfortable couch, covered with rugs, for a period of one to one and a half hours, before the metabolism was examined, and where he continued to rest for the two experimental periods. The trunk and legs were flat upon the couch, the head being slightly raised.

(d) The external temperature was maintained as uniform as possible, though the room was not well suited for this purpose, and ranged between $16^{\circ}C.$ and $20^{\circ}C.$, the majority of the experiments being carried out with an external temperature of between $17^{\circ}C.$ and $19^{\circ}C.$ The body temperature was taken by the mouth just before the first metabolism was taken.

The subjects examined. Fifty-one subjects were examined, and of these five were rejected for the following reasons:

Nos. 1 and 2 as being definite cases of hyperthyroidism—both on clinical grounds and as confirmed by their metabolic rate, which in each case, and by all three methods of calculation, exceeded the normal by 20 per cent. or over.

No. 9. Measurement of the O_2 consumption of this subject with accuracy was impossible, owing to the fact that his respiration-rate was $2\frac{1}{2}$ –3 breaths per minute, and the volume of the respirations highly variable.

No. 15. A highly neurasthenic subject, who was sleeping badly, taking very little food, and abnormally thin, even as compared with his own weight in health. By all three methods of calculation his metabolic rate was over 15 per cent. below normal.

No. 35, a subject who had been under treatment for exophthalmic goitre, who still showed definite exophthalmos and suffered from attacks of paroxysmal tachycardia, and by Dreyer's method showed a metabolism of +16.3 per cent.

Of these rejected subjects, Nos. 1, 2, 15, and 35 were known to be abnormal before the examinations were made.

The remaining forty-six subjects who have been examined were all apparently normal individuals, comprising residents in the University, undergraduates and fellows of colleges, boys attending secondary schools in the neighbourhood, and one or two working men and elementary schoolboys. Their previous medical history was inquired into, and was good with the exception of one, a medical student, No. 28, who had had rheumatic fever. An aortic regurgitant murmur was found on examination, of which the subject was unaware. The attack of acute rheumatism had occurred six years ago; the heart was normal in size, the exercise tolerance was normal, and the subject accustomed to take active exercise without distress. He has therefore been included in the series.

A detailed table of all the observations made upon the forty-six subjects included in the present series is given in Appendix II, A and B.

For purposes of calculation of the normal by the three methods at present available the following procedures were adopted, though it must here be mentioned that Dreyer's method *alone* offers a basis for determining the normal basal metabolism over the whole range covered: this method, therefore, is taken first.

Dreyer's method. The method offered by Dreyer is intended to cover the whole range of normal individuals from 5 years upwards, as stated in his preliminary communication, and expresses the fact that the basal metabolism is a function of the weight and the age of males in the formula:

$$\frac{W_n}{C \times A^{0.1333}} = K,$$

where W = the net body-weight in grammes, C = total number of calories produced in 24 hours, A = age in years, and K is a constant.

In the above-mentioned formula, as determined from Benedict's series—in

which the observed weight alone was available—'n' is approximately 0.5, and $K = 0.1015$. Dreyer states that the deviations from his formula which occur when using the observed weight will be considerably reduced when the calculated weight or 'normal weight' is employed. The calculated weight is determined by averaging the weights corresponding to the individual's trunk length and chest circumference, which can be ascertained from the tables already published. In these tables it has been shown that:

$$(i) \frac{W_n}{\lambda} = K \text{ where the power 'n' in males is 0.319, and the constant } K \text{ is 0.38025.}$$

$$(ii) \frac{W_n}{Ch} = K \text{ where the power 'n' in males is 0.365, and the constant } K \text{ is 0.662.}$$

In the above formulae W = net body-weight in grammes, λ = trunk length in centimetres, and Ch = chest circumference in centimetres.

In the present series, therefore, the calculated weight has been used and the percentage deviation calculated in each instance, using $K = 0.1015$, and also using the mean K determined for the whole series, which was 0.0990. The exact value of 'n' and K when the calculated weight is employed will require a far more extensive series of observations than the present series to establish, but it is worth mentioning that the best 'n' determined by the graphic method for the present series, and using the calculated or normal weight in each case, was found to be 0.5 as originally determined by Dreyer.

If the observed weight and not the calculated weight be employed in the present series, the mean percentage deviation is 7.27 per cent., disregarding sign, and the mean K is 0.0961, or a mean deviation of +5.62 per cent., as compared with Benedict's series, where the mean K is 0.1015.

The mean K of 0.0990 determined for the present series, taking $n = 0.5$, shows a +2.50 per cent. mean deviation upon the K of 0.1015 determined for Benedict's series, a fact which may be explained either by lack of the necessary measurements with which to control the weight measurements of Benedict's series, by a small positive error in the O_2 values given by the calorimeter, or by reason of the present series of observations having been carried out upon subjects who may be regarded as athletes. All observers are agreed that athletes have a metabolism greater than the metabolism of persons leading a sedentary life, and the high proportion of subjects showing more than an A class vital capacity in the present series supports the view that the present series are of an athletic type. It is not unreasonable to suppose that when a sufficiently large number of individuals have been examined, it will be found that the population may be grouped in metabolic levels, much as it has been found possible to do in the case of the vital capacity and physical fitness. In the case of the vital capacity it has been clearly shown that individuals living under ideal nutritional and environmental conditions have a larger vital capacity than those who are less fortunately placed.

Group differences in metabolic rate will find their numerical expression in the K of Dreyer's formula.

Benedict's method. Benedict and Harris have constructed multiple prediction tables as a guide to the clinician and physiologist, but themselves state, with regard to these tables, which cover only a limited range of age and weight, that they do not fully represent the metabolism of the developmental period, and that they have depended upon a number of observations for their construction which, biometrically considered, is small.

(a) For purposes of comparison in the present series the multiple prediction tables have been employed over their published range from 21 years of age upwards.

(b) Over the ages not covered by these tables, nor by the tables published by Benedict and Talbot (7) for boys from body-weight alone, it has been necessary to extend the use of the formulae employed in the construction of the multiple prediction tables downwards to cover the gap. Therefore, for those subjects whose weight is below 38 kilos, the tables of Benedict and Talbot for boys have been employed. Above that weight the normal has been calculated from Benedict's formula until the multiple prediction tables could be used.

Benedict and Harris's formula upon which their multiple prediction tables are based is:

Where H = heat-production per 24 hours,
 W = weight without clothes in kilos,
 S = stature in centimetres,
 a = age in years,

Du Bois's method. This depends upon the determination of the surface area of each individual and the use of tables giving the heat-production per square metre for individuals of different ages and of the two sexes. Du Bois's formula for calculating the area in square centimetres is:

$$\text{Area (square centimetres)} = W^{0.425} \times H^{0.725} \times 71.84.$$

Where W = weight without clothes in kilos,
 H = standing height in centimetres,

This method, again, is advanced by its supporters as applicable only down to 14 years of age, so that in four instances in this series the normal cannot be calculated, and in three other instances the calculation has been made when the boys were in their fourteenth year by using Du Bois's value for boys from 14 to 16 years of age.

To some extent liberties have been taken in determining the normal by the methods of Benedict and Du Bois in the present series, but the mean deviation between observation and prediction, adhering strictly to their published tables, is also given. It must be admitted that their methods have an inherent weakness in the strict limitation of their application as compared with Dreyer's method. The metabolism of the new-born infant, and the earliest years of life, when the child is growing at an enormous pace, and changing from a poikilo-

TABLE I.

Serial No.	Age.	Height.	Observed Weight.	Calc. Weight.	Observed Calories per 24 hours.	Dreyer Mean % Δ $K = 0.1015$.	Dreyer Mean % Δ own series. $K = 0.0990$.	Benedict Mean % Δ .	Du Bois Mean % Δ .
3	23	179.5	58.6	69.45	1758	1666 + 2.85	+5.4 + 0.31	+ 8.90	+ 6.25
4	26	163.3	47.75	54.27	1482	1544 - 0.30	-3.9 - 2.7	+ 8.50	+ 4.60
5	21	173.0	54.6	57.05	1688	1620 + 7.6	+13.7 + 4.8	+ 9.45	+ 7.90
6	30	182.1	76.8	80.30	1777	1865 \pm 0.00	-4.8 - 2.4	- 3.00	- 5.30
7	21	171.3	67.0	68.78	1782	1780 + 3.55	+1.1 + 0.9	+ 4.65	+ 5.20
8	23	175.0	70.7	67.94	1940	1798 + 14.70	+7.8 - 11.8	+ 10.30	+ 10.20
10	21	180.0	73.3	76.12	1812	1826 \pm 0.00	-0.8 - 2.4	- 1.10	- 0.70
11	21	181.4	71.2	81.22	2027	1804 + 8.35	+12.2 + 5.5	+ 12.10	+ 11.90
12	21	178.1	67.8	65.59	1889	1767 + 12.95	+6.8 + 9.6	+ 8.00	+ 7.85
13	15	163.4	52.8	50.50	1603	1600 + 3.80	+0 + 1.2	+ 6.75†	- 6.95
14	16	187.2	65.0	69.80	2050	1735 + 14.90	+12 + 11.9	+ 14.70†	+ 5.60
16	16	164.2	45.5	46.13	1420	1520 - 2.95	-6.6 - 5.3	+ 1.00†	- 6.35
17	34	187.0	77.7	80.24	1779	1874 + 1.90	-5.1 - 0.6	- 3.45	+ 7.55
18	15	157.5	45.9	47.34	1683	1525 + 12.80	+10.5 + 9.8	+ 21.50†	+ 6.55
19	32	185.7	68.8	75.70	1874	1777 + 9.80	+5.6 + 7.0	+ 8.55	+ 3.25
20	32	181.9	57.8	65.83	1562	1656 - 2.45	-5.8 - 4.4	+ 0.50	- 5.90
21	21	173.6	62.5	67.01	1717	1707 + 1.00	+0.6 - 1.4	+ 3.80	+ 1.00
22	29	174.4	67.4	71.06	1841	1761 + 9.80	+4.5 + 7.0	+ 10.15	+ 6.90
23	26	177.4	69.5	72.73	1724	1784 + 0.20	-3.4 - 2.2	- 0.50	- 2.25
24	40	164.9	56.8	63.65	1548	1645 + 1.75	-5.9 - 0.8	+ 10.30	+ 3.20
25	25	173.5	78.5	77.91	1902	1893 + 6.25	+1.1 + 3.6	+ 3.09	+ 4.00
26	22	179.5	71.6	72.41	1767	1807 + 0.60	-2.2 - 1.9	- 1.36	- 1.80
27	38	174.6	78.9	83.80	1700	1888 - 3.25	-10.0 - 5.6	- 3.80	- 7.60
28	22	178.4	58.8	63.05	1639	1667 \pm 0.00	-1.7 - 2.4	+ 2.80	+ 1.40
29	31	168.0	61.15	66.22	1582	1692 - 1.30	-6.5 - 3.3	+ 2.45	- 1.50
30	27	181.2	70.0	81.40	1849	1790 + 2.10	+3.3 - 0.5	+ 5.60	+ 2.80
31	13 $\frac{6}{12}$	149.6	34.8	35.07	1386	1403 + 6.25	+1.2 + 2.3	+ 15.31	+ 2.35†
32	15	168.9	48.5	50.09	1770	1553 + 15.10	+4.2 + 13.1	+ 19.80†	+ 4.02
33	27	183.0	59.1	69.56	1677	1670 + 0.10	+0.4 - 2.3	+ 4.00	- 0.45
34	29	185.0	101.0	94.35	2196	2131 + 13.70	+2.8 + 10.7	+ 0.51	+ 2.53
36	25	176.0	53.21	62.97	1626	1605 + 1.05	+1.3 - 1.4	+ 7.65	+ 3.85
37	36	174.2	63.2	67.54	1737	1715 + 9.00	+1.3 + 6.3	+ 10.80	+ 3.60
38	27	173.4	69.0	69.52	1747	1779 + 4.40	-1.8 + 1.7	+ 2.25	+ 1.00
39	13 $\frac{6}{12}$	158.7	49.4	52.05	1418	1563 - 10.75	-9.3 - 13.6	+ 5.11†	- 13.49†
40	15 $\frac{11}{12}$	162.7	47.0	51.53	1376	1537 - 10.90	-10.5 - 13.3	+ 10.94†	- 16.89
41	14 $\frac{3}{12}$	157.7	50.5	52.96	1491	1575 - 6.15	-5.3 - 8.7	+ 2.50†	- 9.47
42	12 $\frac{3}{12}$	152.3	38.7	39.44	1546	1446 + 10.45	+6.9 + 7.6	+ 21.14†	—
43	11 $\frac{11}{12}$	147.0	39.2	40.51	1447	1451 + 1.30	-0.3 - 2.0	+ 14.20†	—
44	15 $\frac{1}{12}$	156.2	46.8	47.93	1571	1536 + 4.75	+2.3 + 1.8	+ 12.99†	+ 0.80
45	9 $\frac{9}{12}$	133.5	28.2	29.28	1300	1330 + 4.15	-2.2 + 0.6	+ 20.65	—
46	13 $\frac{11}{12}$	144.9	35.0	40.20	1291	1405 - 7.00	-8.1 - 9.9	+ 8.34	- 1.97†
47	30	180.1	69.8	71.60	1604	1788 - 4.25	-0.5 - 7.0	- 6.58	- 10.25
48	16 $\frac{3}{12}$	171.2	54.5	57.19	1581	1620 - 5.45	-5.6 - 8.50	- 1.80†	- 9.25
49	17 $\frac{11}{12}$	179.0	53.8	64.75	1673	1667 - 2.60	-0.4 - 5.0	+ 1.03†	- 7.11
50	15 $\frac{1}{12}$	151.6	38.6	40.84	1563	1445 + 12.90	+8.4 + 10.24	+ 22.59†	+ 9.53
51	12 $\frac{11}{12}$	148.4	33.2	37.04	1363	1385 + 0.80	-1.4 - 1.7	+ 15.51	—

Using only observations exactly covered by published tables	Mean % Δ	=	5.58 %	5.20 %	8.04 %	5.51 %
	No. of observations	=	46	46	46	42
	Individual mean \pm % Δ	=	5.58 %	5.20 %	6.69 %	5.48 %
	No. of observations	=	46	46	32	39

Nos. 1, 2, 9, 15, and 35 are subjects excluded from present series for reasons stated.

† Subjects not exactly covered by published tables.

+15 +13 +15 +12
 -11 -13 -7 -16
 +504
 46 231.2 (21)
 (-7)

thermic to a homoiothermic individual, undoubtedly presents a special problem of its own. When, however, we begin to consider the child of 5 years and upwards the problem would appear to be a simpler one. It is clear that when a formula expresses a biometric law, which relates metabolism to body size and age, and yet covers *the whole period of growth, adult life, and senescence*, with a low mean error between calculation and observation, then such formula must be regarded as more satisfactory than formulae which require continual readjustment with the changing of the factors under consideration, even though smaller limits of variation may be secured over the limited ranges covered. In this respect Dreyer's formula stands distinguished from those of Benedict and Du Bois, and, moreover, as shown in the analysis of the present series, it stands the test of comparison well, even within the self-imposed limits of these observers. The analysis of all available observations given in Dreyer's preliminary communication further shows that *his formula is over all ages an improvement upon the other two methods*.

In Table I the details of the forty-six subjects are shown *in extenso* with the mean percentage deviation calculated individually by each of the three methods. It will be seen that in this series Du Bois's method of calculation has a slight advantage over Dreyer's method, when for the purpose of calculation Dreyer's K of 0.1015 is employed, but that Dreyer's is slightly the better method when the mean K of the series 0.0990 is employed.

The advantage secured by Du Bois's method must, however, be regarded as apparent only, for reasons already advanced in this paper, namely, that this method is only limited in application. Further, as Benedict and Harris point out in their admirable treatise on basal metabolism, the true test of any method for the reduction of the metabolism of individuals of different size and shape to comparable terms is:

(a) Its capacity for predicting an unknown metabolism.

(b) Its capacity to determine the value of the deviation from the normal in pathological states.

The theoretical question of the normal must be settled before any medical significance can be attached to the deviations met with in pathological states.

While the methods of Benedict and Du Bois, applied over their own limited ranges, may be considered to fulfil condition (a) with considerable success, from a theoretical and practical point of view they fail to fulfil condition (b), in that only the crudest tests are available to estimate the normality of the weight of the subject, which in diseased conditions may show marked changes, and upon the observed weight alone can they depend in their formulae.

In Table II the forty-six subjects examined are grouped according to age, and the percentage deviation for each group shown, as determined by the three methods, using only those observations strictly comparable by each method.

TABLE II.

Grouping by Age, disregarding Sign.

Age.	No.	K = 0.1015 Dreyer.	K = 0.0990 Dreyer.	No.	Benedict.	No.	Du Bois.
Years.		% Δ.	% Δ.		% Δ.		% Δ.
< 15	8	5.87	5.86	4*	14.43	—	—
15-20	10	8.63	8.06			10	7.31
20-25	10	5.17	4.15	10	6.30	10	5.42
25-30	9	4.21	3.62	9	4.64	9	3.10
30-40	9	3.75	4.18	9	5.53	9	5.34
	46			32		38	

* Benedict and Talbot, *Carnegie Inst., Wash., Pub. No. 302*, 1921, Table 36, p. 206.

In the above table only those observations strictly covered by published tables of the three authors have been used.

It is interesting to note that the mean deviation disregarding sign shows a distinct tendency to diminish with increasing age, a fact which would suggest that the 'physiological state' of the individuals in the active developmental period is more variable than in the adult. That this is the case not only in early life but also in senescence is further supported by the observations of Benedict analysed by Dreyer, and published in the table given in Dreyer's preliminary communication and analysis.

TABLE III.

Grouping by Weight, disregarding Sign.

Weight in kilos.	No.	K = 0.1015 Dreyer.	K = 0.0990 Dreyer.	No.	Benedict.	No.	Du Bois.
		% Δ.	% Δ.		% Δ.		% Δ.
25-30	1						
30-35	2						
35-40	4	6.13	4.95	4*	14.43	(1	9.53)
40-45	—	—	—	—	—	—	—
45-50	6	8.82	9.69	1	8.50	5	7.68
50-55	6	4.81	4.45	2	8.05	6	6.38
55-60	6	1.64	2.58	5	5.30	6	4.00
60-65	4	6.58	5.79	3	5.78	4	2.93
65-70	7	6.42	5.09	7	5.88	7	5.29
70-75	5	5.15	4.47	5	6.19	5	5.38
75-80	4	2.35	3.09	4	3.34	4	6.11
100-105	1	13.70	10.74	1	0.51	1	2.53
Totals	46			32		39	

* Benedict and Talbot, *Carnegie Inst., Wash., Pub. No. 302*, 1921, Table 36, p. 206.

In the above table only those observations strictly covered by published tables of the three authors have been used.

Table III shows the percentage deviation of the weight groups, using only those observations which are strictly comparable.

In all the above-mentioned tables it will be seen that Dreyer's method not only covers a greater range than the other two methods, but in addition shows in almost every instance a closer correspondence between prediction and observation.

TABLE IV. *Age, Occupation, Physical Fitness, Nutrition, Haemoglobin, Blood-pressure (Lying), Pulse-rate, and Exercise Tolerance of Subjects examined.*

Initials.	Series. No.	Occupation.	\pm % Δ Obs. Wt. from Calc. Wt.	Phys. Fitness Class.	Age.	Hb. Units.	Blood-pressure.		Pulse.		Following Exercise, Pulse, and Recovery Time.
							Sys.	Di.	Ly.	St.	
D. D.	3	Golf pro.	-15.7	A - 2.9	23	211	115	75	73	88	120, 2 min.
W. E. B.	4	Labourer	-12.0	A + 7.0	26	190	116	70	61	80	144 "
T. E. T.	5	Undergrad.	- 4.3	B - 0.2	21	198	110	80	68	84	128 "
F. G. H.	6	Physician	- 4.3	A + 17.5	30	205	120	75	56	+	Normal
E. L. F.	7	Med. student	- 2.5	A + 2.3	21	186	128	75	48	+	Normal
F. G. M.	8	Undergrad.	+ 4.2	A - 0.5	23	185	129	80	67	80	140, 2 min.
L. G. C.	10	Undergrad.	- 3.7	A + 13.5	21	196	120	74	44	58	108 "
P. C. M.	11	Med. student	-12.3	A + 26.1	21	189	123	80	50	80	116 "
H. L.	12	Undergrad.	+ 3.4	A + 17.4	21	191	122	80	60	84	124 "
F. W.	13	Schoolboy	+ 4.6	B + 1.3	15	176	112	76	62	99	136 "
C. G.	14	Schoolboy	- 6.9	A + 4.9	16	184	110	72	69	71	108 "
F. G. T.	16	Schoolboy	- 1.4	A + 2.0	16	185	114	70	66	92	132 "
H. K. W.	17	Res. worker	- 3.1	A + 2.8	34	184	112	68	68	78	116 "
A. L. F.	18	Lab. boy	+ 0.7	B - 4.3	15	184	114	70	62	+	Normal
R. B. B.	19	Coll. tutor	- 9.1	A + 15.2	32	173	118	84	60	74	112, 2 min.
W. T. C.	20	Physician	-12.2	A + 19.1	32	178	110	76	46.5	82	104 "
H. A.	21	Lab. asst.	- 6.7	A + 5.6	21	189	140	86	62.5	74	96 "
J. W.	22	Lab. asst.	- 5.2	A - 0.4	29	190	120	78	74	86	116 "
H. N. S.	23	Med. student	- 4.3	A + 2.9	26	192	125	82	60	68	96 "
P. G.	24	Labourer	-10.6	A - 3.8	40	193	130	80	62.5	70	108 "
E. A. C.	25	Med. student	+ 0.8	A - 2.0	25	179	126	72	65	76	108 "
R. L. V.	26	Res. worker	- 1.1	A + 16.2	22	171	126	78	51	60	100 "
A. D. G.	27	Res. worker	- 5.9	A + 2.4	38	186	126	80	50	+	Normal
M. S. W. M.	28	Med. student	- 6.6	A + 3.8	22	186	122	65	68	82	128, 2 min.
A. C.	29	Lab. asst.	- 7.5	A + 1.5	31	193	122	80	58.5	72	96 "
M. H. M.	30	Coll. tutor	-14.0	A + 37.4	27	184	127	88	79	+	Normal
H. W.	31	Schoolboy	- 0.7	C - 4.7	13 $\frac{1}{2}$	175	122	78	80	+	Normal
F. G.	32	Lab. boy	- 2.9	B + 0.1	15	187	140	82	75	106	136, 2 min.
F. G. T. L.	33	Coll. tutor	-14.2	A + 16.8	27	188	135	95	61	64	104 "
J. B. S. H.	34	Coll. tutor	+ 7.0	A - 1.3	29	184	107	70	60	66	100 "
C. N. H.	36	Coll. tutor	-15.8	A + 14.6	25	194	105	75	61.5	+	Normal
W. W. W.	37	Surgeon	- 6.5	A + 4.8	36	173	116	78	60	74	104, 2 min.
R. S.	38	Tech. engineer	- 0.7	B - 4.5	27	190	128	80	65.5	76	96 "
G. P.	39	Schoolboy	- 5.8	A - 1.4	13 $\frac{1}{2}$	191	134	84	51.5	70	132 "
P. J. K.	40	Schoolboy	- 8.7	A + 4.3	15 $\frac{1}{2}$	179	108	60	54	78	112, 1 min.
R. D. K.	41	Schoolboy	- 4.6	B + 2.7	14 $\frac{1}{2}$	175	—	—	59	66	112 "
N. W.	42	Schoolboy	- 1.8	A + 3.7	12 $\frac{1}{2}$	171	112	70	63.5	84	120, 2 min.
H. P.	43	Schoolboy	- 3.1	B + 0.4	11 $\frac{1}{2}$	180	120	80	66.5	80	132, 1 min.
Hugh P.	44	Schoolboy	- 2.2	A - 4.9	15 $\frac{1}{2}$	179	118	66	67.5	102	136, 2 min.
S. W.	45	Schoolboy	- 3.6	C - 4.6	9 $\frac{1}{2}$	172	100	64	64.5	88	100 "
J. W. E. T.	46	Schoolboy	-12.9	C - 3.2	13 $\frac{1}{2}$	172	128	78	65.5	—	—
E. S. S.	47	School- master	- 2.5	A + 18.2	30	187	112	72	57.5	80	96 "
H. W.	48	Lab. boy	- 4.5	A + 7.1	31 $\frac{1}{2}$	185	110	70	57	68	100 "
C. R. L.	49	Lab. boy	- 9.2	B + 0.8	17	182	120	78	63.5	74	116 "
S. B.	50	Lab. boy	- 5.5	A + 7.4	15 $\frac{1}{2}$	187	116	76	82	86	116 "
C. B.	51*	Schoolboy	-10.3	A - 0.7	12 $\frac{1}{2}$	—	—	—	77	—	—

* Nearly fainted when haemoglobin sample was taken—hence only one metabolism test and no pulse or haemoglobin records.

+ Standing pulse-rate and response to exercise tested on other days and therefore not comparable with lying pulse-rate in table.

In Table IV are shown the observations upon the forty-six subjects covering their examination in other respects than metabolism.

When examined by the method of least squares the present series of observations show a mean percentage deviation and distribution of errors as under :

Distribution of Errors.

Dreyer K = 0.0990, by Method of Least Squares.

	Theoretical Distribution.	% Δ .	Distribution of Present Series.	
	%		No.	%
Within 0.5 mean Δ	38.3	3.28	21	45.7
" 1.0 " "	68.3	6.56	30	65.2
" 1.5 " "	86.6	9.84	37	80.4
" 2.0 " "	95.4	13.12	43	93.5
" 3.0 " "	99.7	19.68	46	100.0
" 4.0 " "	99.99	26.24	46	100.0
The mean deviation = 6.56.				

TABLE V.

Analysis of Certain Aspects of Table IV.

(i) *Nutrition according to Dreyer's Standards.*

\pm % Δ .	Number.	Description.	%
< 5	23	Normal	50.0
5-10	13	Possibly abnormal	28.2
10-15	8	Probably abnormal	17.4
> 15	2	Certainly abnormal	4.4
Total	46		100.0

(ii) *Physical Fitness according to Dreyer's Standards.*

Number.	Class.	%
35	A	76.1
8	B	17.4
3	C	6.5
Total	46	100.0

A class greater than + 5 % = 28.2 %.

(iii) *Grouping Haemoglobin Unit Value by Age.*

Age.	No.	Units.	Individual % Δ from Group Mean.
< 15 years	7	176.5	2.87
15-20 "	10	182.8	1.66
20-25 "	10	190.2	3.68
25-30 "	9	185.6	2.41
30-40 "	9	185.6	4.22

Table V gives an analytical summary of certain aspects of Table IV.

(a) *Weight.* The series here considered shows a rather higher proportion of

individuals with more than a 10 per cent. deviation between calculation and observation than is usually met with in a sampling from a good class population. This is very largely accounted for by the fact that the series comprises athletic individuals whose chest development is greater than the average, and whose calculated weight by Dreyer's tables tends, therefore, to be on the + side. The series may even so be considered as a fair sampling of a good class of the population.

(b) *Physical fitness.* The series comprises a number of individuals who fulfil Dreyer's standards more than usually well. As will be seen, 76 per cent. are classed as A class, and of these 28.2 per cent. show a vital capacity more than 5 per cent. better than A class. Only two subjects, Nos. 5 and 38, show a B class vital capacity, who might reasonably be expected to show an A class vital capacity. Of these, No. 5 had had rather less than the usual amount of athletic training at his preparatory and public school, owing to a 'weak heart'. No indications of any cardiac insufficiency could be detected, either objectively or subjectively, and he was in the habit latterly of bicycling distances of 50-60 miles in a day for two or three days consecutively. No. 38 had been gassed during the war—with some involvement of the lungs—and he suffered from a mild chronic laryngitis which has never caused him anything more than passing inconvenience for the past three years.

The remaining six subjects who show a B class vital capacity, and the three who show a C class vital capacity, are all in the occupational groups, the individuals of which would be expected to be in these categories, as shown in Dreyer's provisional classification in his tables.

From this point of view, therefore, the series may be considered to comprise individuals who are all at least normally fit for their conditions of life and occupations.

Haemoglobin percentage. The diurnal variations already demonstrated by Dreyer, Bassett, and Pierce rob any individual observation of its absolute value; moreover, although two observations have been taken in nearly every case, it is realized that these observations have been taken at a time of day when the variations from hour to hour may be of some magnitude. Two further observations of different individuals have been taken to emphasize this point, and are shown in Fig. 1.

For purposes of Table IV the mean value of the two readings has been taken and is expressed in units; the numerical value of these units as compared with the Haldane standard can be determined from the comparative table in Appendix III.

As Williamson (8) has shown in America, there are variations in the haemoglobin percentage apparently most closely correlated with age; the lower values, therefore, met with in some of the younger individuals can be regarded as 'normal'.

As a whole the series will be seen to be not deficient as regards the haemoglobin content of the blood of each individual measured.

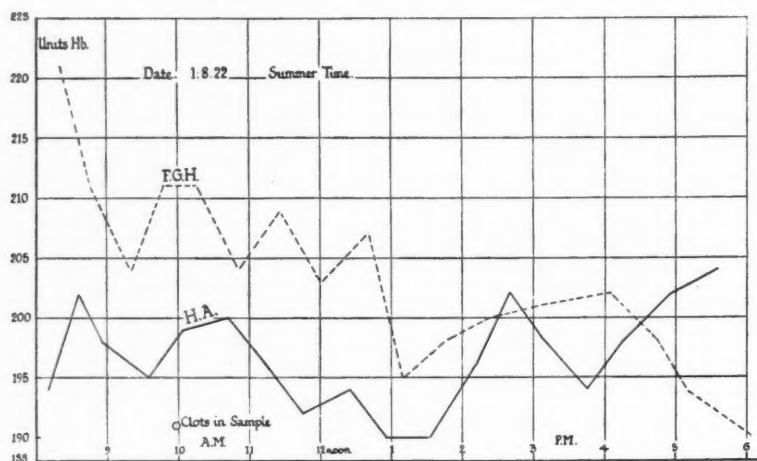


FIG. 1.

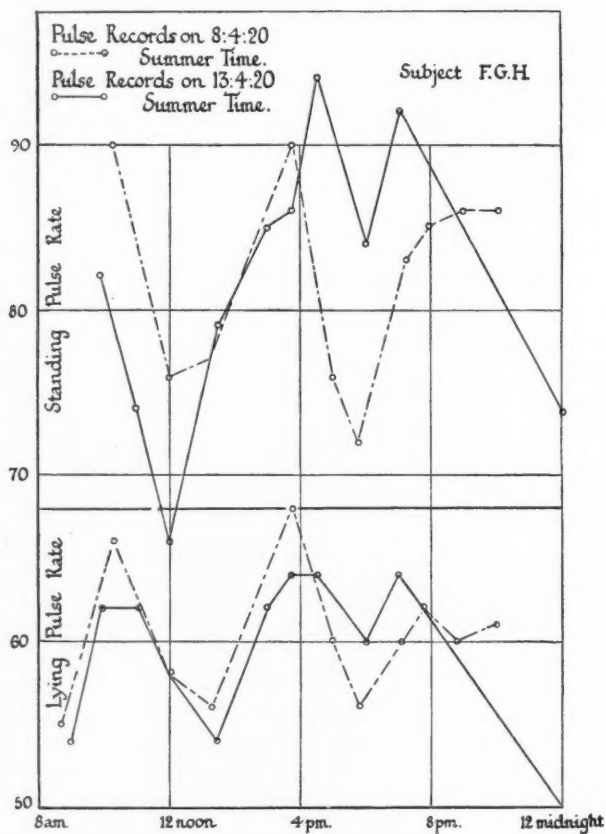


FIG. 2.

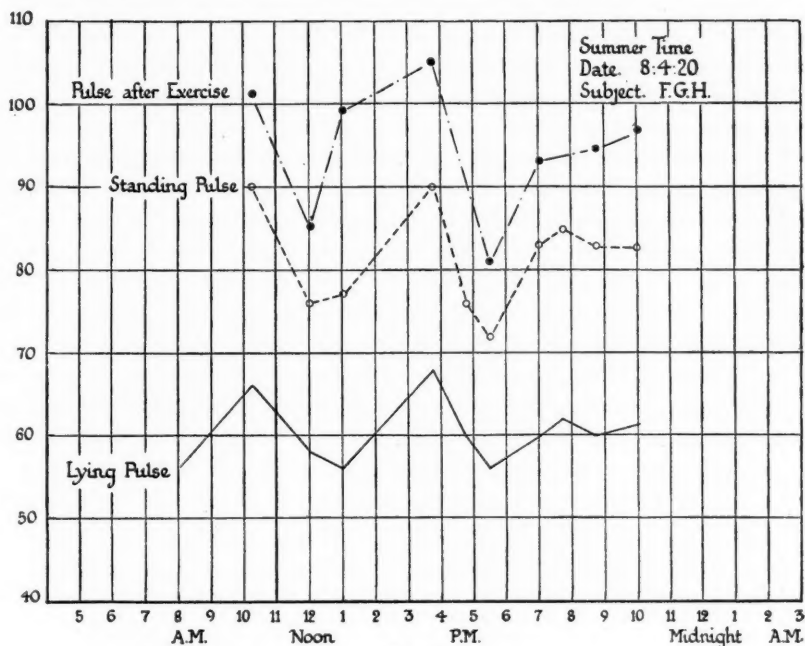


FIG. 3.

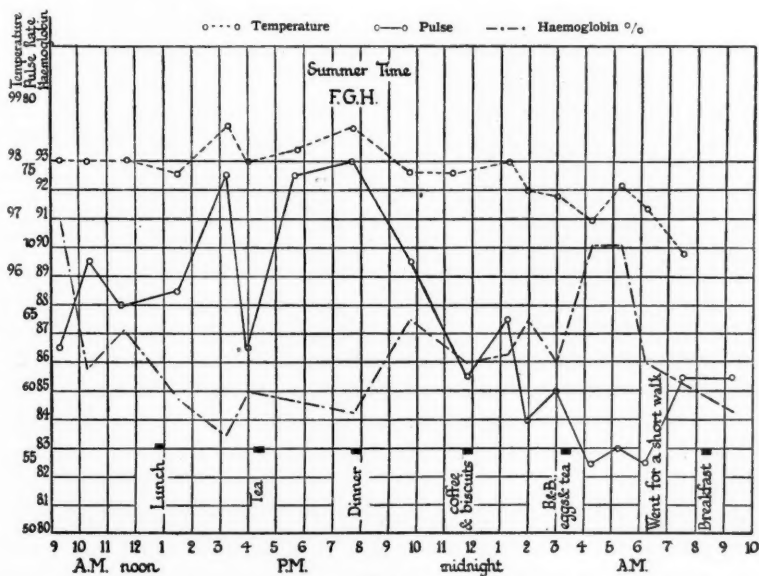


FIG. 4.

Pulse-rate. No absolute values can be attached to the observations, since we have nothing but the crudest guides as to the 'normal' pulse-rate. Diurnal variations of pulse definitely occur, as is shown in Figs. 2 and 3, from the same subject on different days; and that these variations occur in the opposite sense to the variations which occur in the haemoglobin content of the blood is shown in Fig. 4, from the same subject as Figs. 2 and 3. More factors, however, enter into adjustment of the pulse-rate than can be here considered. That such variations should occur was indicated in the paper already mentioned.

Every metabolism experiment carried out has shown that, even in the most unemotional of subjects, a small emotional disturbance is incidental to their attachment to the machine, in the raised pulse-rate met with in the first few minutes, which occurred without exception. The pulse rapidly settled down and remained steady during the remainder of the period; moreover, the average pulse-rate during the second metabolic period was in almost every instance lower than the average of the first period.

No comparative value can, however, be attached to these, because (1) it is impossible to exclude the persistence of some mild psychological element; (2) time has passed and the rate will have changed through the influence of other factors, such as haemoglobin percentage, &c.

Lying pulse-rate. However, for what it is worth, the average pulse-rate during the second metabolic period is given. The average is derived from the pulse-rate taken in the first, fifth, ninth, and twelfth or thirteenth minutes of the experiment, and, as already mentioned, rarely showed the rise the first minute invariably met with in the early minutes of the first period.

Standing pulse-rate. Similar factors enter into the determination of the standing pulse-rate, though their effect may be even more marked upon the rate than in the case of the lying pulse.

Pulse-rate after exercise. Similar factors again affect the actual rate at different times of day, with the possible exception that the rate determined immediately upon the completion of an exercise is probably but little interfered with by psychological disturbances, which in lying or standing positions may produce distinct effects. Figs. 2 and 3 show what variations may occur in the lying and standing pulse-rates, with the pulse-rate taken immediately following standard exercise at different hours of the day in the same individual. Moreover, at different rates the pace of recovery of the pulse after exercise may be inconstant, though conforming always to Lewis's requirements of normality in that it has returned to normal within two minutes from ceasing the exercise.

Bearing the above-mentioned facts in mind, it is impossible to attach anything but a general value to the observations made upon the individuals in this series.

As regards the exercise performed, it should be noted that while the rate of performance was controlled, and the height of the chair constant, the amount of work involved for each individual cannot be regarded as identical in view of (1) the differences in weight, (2) the differences in the leg-length of the individuals.

Compare, for instance, Nos. 17 and 45. No account is given to the considerations of weight, length of leg, or muscular development in Lewis's published figures for the 'normal young man'.

Blood-pressure. Here, again, our standards of normality are but of the most approximate order, the actual reading in any one individual shows diurnal variations of some magnitude. This point might be of some interest to the assessors in the renal clinics of the Ministry of Pensions, where comparative values are attached to observations of the blood-pressure for purposes of grading the pensions. Under these circumstances a man may secure a 5 per cent. higher pension at 10 a.m. than he would at 2 p.m. the same day.

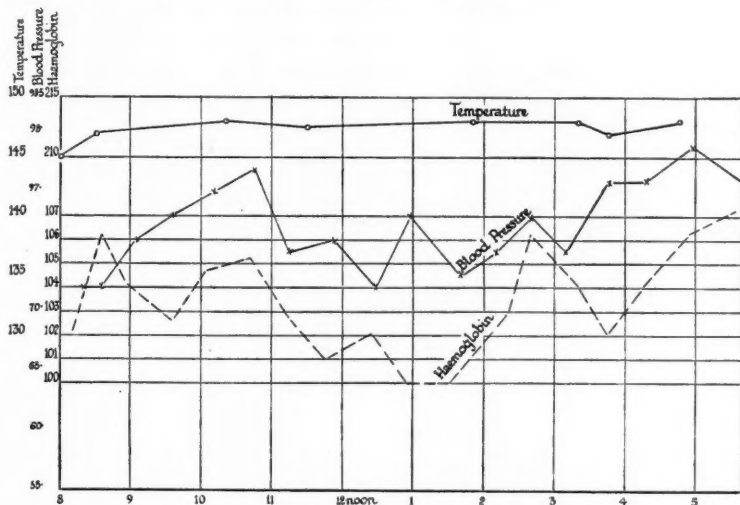


FIG. 5.

That these diurnal variations are associated with the variations in the concentration of the blood is suggested by Fig. 5, but again it is certain that other factors than the concentration of the blood enter into the question.

In each individual of the present series the systolic and diastolic blood-pressure determined by the auscultatory method after the completion of the second metabolic period is shown. In this respect it will be seen that quite a number of the subjects examined show a systolic blood-pressure which might be regarded as high.

Conclusions.

1. That Dreyer's formula, $\frac{W^n}{C \times A^{0.1333}} = K$, where n is approximately 0.5 and $K = 0.1015$ in males, expresses the basal metabolism in an extremely satisfactory manner over a wide range of body size and age, as claimed by its author in his preliminary communication.

2. That, as predicted by Dreyer in his preliminary communication, a definite and important improvement between calculation and observation is secured when the normal weight (calculated) in place of the observed weight is used for purposes of calculation.

3. That healthy individuals whose observed weight shows considerable deviations from their calculated weight may have a metabolism which is entirely normal, considered in relation to their calculated weight.

4. Both from a theoretical and practical standpoint the calculated weight and not the observed weight should be employed in calculation of the normal basal metabolism for any given individual.

5. That for individuals leading a healthy active life, with opportunities for physical recreation, the K in Dreyer's formula will be found to be approximately 0.0990 instead of 0.1015.

6. That as a method of calculating the basal metabolism Dreyer's formula fulfils all the necessary criteria in a highly satisfactory manner both from theoretical and practical considerations. That it is an improvement upon the methods of Benedict and Du Bois, in that it holds over a wider range of age and weight with greater accuracy, and is based upon sounder principles.

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APPENDIX I.

The Benedict clinical calorimeter, as supplied by the Sanborn Company, shows poor workmanship in all its details, and in certain respects its deficiencies render rapid and accurate working wellnigh impossible.

The defects particularly noted and remedied were as follows:

1. The milled head which opens and closes the valve connecting the subject with the calorimeter is difficult to manipulate with accuracy and speed, an important defect, since the value of the spirometer readings depends upon the opening and closing of the valve exactly at the end of an expiration.

By attaching a short lever arm to the milled head, which in the horizontal position showed that the valve into the circuit was shut, and in the vertical position open, it was possible to remedy this defect. Manipulation of the valve

was certain and rapid, and with care the valve could be opened and closed accurately to coincide with the end of an expiration.

2. The valve itself offers a somewhat small aperture through which the subject has to breathe in the open air, and a distinct impression of resistance to normal inspiration and expiration is noted by subjects who are at all quick or deep breathers. When the valve is open into the circuit this resistance is negligible, since the right angle turn which the breath has to take when the valve is open to the external air is eliminated. This particular defect was not considered to be of sufficient magnitude seriously to disturb normal subjects, but might well be a factor of some magnitude in neurotic subjects.

3. The air-pump provided with the machine was found to be capable of delivering 15 litres of air per minute through the resistance offered by the soda lime and calcium chloride jars. This supply was considered to be too small, and, further, the pump was found to be extremely roughly made and liable to break down. The flanges of the fan on examination were found to be of soft copper roughly bent into a scoop shape, and with their extremities at unequal distances from the casing. At a high speed of rotation these flanges weakened at the point of bending and allowed the scoops to strike the case. A new fan was fitted with six phosphor-bronze flanges, allowing a millimetre of free space between the fan and the casing. The new fan was found to deliver 30 litres of air per minute through the resistance of the bottles, and to be quieter in its working.

4. When it is desired to weigh the CO_2 absorbing bottles, the soda lime bottle and the second calcium chloride bottle, the connexions provided between these bottles are extremely clumsy, unsatisfactory, and unduly heavy.

In the first place it was found extremely difficult to secure an air-tight circuit when reconnecting the bottles after weighing, and it was essential to make repeated tests and adjustments before the circuit could be considered air-tight.

In the second place the nuts attaching the connecting pipes to the bottles are made of soft brass, fragments of which are liable to be removed when any force is used with a spanner. The weight, therefore, of the bottles after manipulation is liable to be affected. This serious defect was remedied by constructing new caps for the bottles of a much lighter pattern, with tapered conical ends where the conducting pipes projected from the caps. This enabled metal pipes with stout rubber connexions to be employed to connect the bottles. These could be quickly applied to and drawn off the conical ends, and required a minimum amount of manipulation. After these were introduced no difficulties owing to leaks were encountered. Rubber corks, two for each bottle, were attached by threads to the cap of the bottle, and inserted into the openings of the pipes when the bottles were disconnected with the machine—the possibility of further CO_2 and water being absorbed from the air was thus eliminated.

5. The noise and vibration of the machine when the motor is running are considerable, and capable of being an unnecessary disturbing factor in the case of a highly-strung subject. A very marked improvement in these two respects was secured by (a) mounting the motor, air-pump, and bottle-grips on stout pieces of rubber, (b) by mounting the spirometer on four iron legs firmly screwed to the wooden platform in place of the ring seating attached to the central iron standard.

A later improvement has been to fit the wooden platform with iron feet, each of which is equipped with an adjusting screw with a metal disk to stand on the ground. By this means the platform can be raised off the wheels, and the apparatus adjusted so that the bell of the spirometer can rise and fall free from contact with the walls of the water-jacket.

Specimen Page of Experimental Records.

No. 10.

Name, L. G. C.

Age, 21 $\frac{2}{3}$.

Height, 180.0 cm.

A, 93.9 cm.

Chest, 92.5 cm.

Obs. wt., 73.3 kilos.

V. C., 5380 c.c.

Date, 16.12.1921.

Diagnosis, Normal.

		Time.	Start	Finish	Oxygen.	Test No. 1.	Test No. 2.
Du Bosq Readings		Duration				15' 0"	14' 58"
Haemoglobin.		Spirometer Scale.					
1. 9-9	1. 9-7	Start			8170		8140 c.c.
2. 9-6	2. 9-65	Finish			4160		4040 c.c.
3. 9-7	3. 9-6	Oxygen consumed			4010		4100
4. 9-75	4. 9-65	Temperature.					
5. 9-80	5. 9-65	Start			18-0° C.		18-5° C.
Av. = 9-75	Av. = 9-65	Finish			18-0° C.		20-0° C.
Un. = 195	Un. = 197				18-0° C.		19-0° C.
		Room temperature =			18-0° C.		18-5° C.
		Room barometer =					760 mm. Hg.
		Patient's body temperature =			97-6° F.		Test No. 1.
		Patient's body temperature =					Test No. 2.

*Before Test.**During Test.*

Time.	Pulse.	Resp.	B. P.		Time.		Pulse.	Resp.
1.	54		Sys.	123	1.	1st 2nd	50	16
2.	48		Dia.	70	2.	4th 5th	50	17
3.			Pulse	48	3.	10th 11th	48	16
4.					4.	13th 14th	46	16
Aver.			Hb. sample	10.50 a.m.	Aver.			
1.			Sys.	120	1.	2nd 3rd	44	16
2.			Dia.	74	2.	6th 7th	44	14
3.			Pulse	42	3.	9th 10th	44	16
4.					4.	12th 13th	43	18
Aver.			Hb. sample	11.25 a.m.	Aver.			

No. 1.

Carbon Dioxide.

No. 2.

<i>Before Test.</i>		<i>After Test.</i>		<i>Before Test.</i>		<i>After Test.</i>	
Wt. soda lime	= 2067.70	Wt. =	2074.20	Wt. =		Wt. =	2079.60
Wt. cal. cl.	= 2156.29	Wt. =	2156.80	Wt. =		Wt. =	2158.30
Combined wt.	4223.90		4231.00				4237.90

Combined weights after = 4231.00
 before = 4223.90

after = 4237.90
 before = 4231.00

Grm. CO₂ 7.10 Grm. CO₂ 6.90

Remarks.

Good subject. Response to exercise. Standing pulse = 58. No distress on exercise.
 After exercise = 108. 2 min. later = 56.

APPENDIX II A.

Date.	Serial No.	Sex.	Age.	H.	W.	λ .	Ch.	V.C.
20.11.21	3	M	23	179.5	58.6	90.6	90.0	4260
23.11.21	4	"	26	163.3	47.75	83.0	83.0	4000
9.12.21	5	"	21	173.0	54.6	90.1	78.0	3520
23.12.21	6	"	30	182.1	76.8	94.8	95.0	5800
7.12.21	7	"	21	171.3	67.0	92.8	87.0	4500
22.5.22	8	"	23	175.0	70.7	89.2	90.5	4320
16.12.21	10	"	21	180.0	73.3	93.9	92.5	5380
22.12.21	11	"	21	181.4	71.2	96.0	94.5	6250
2.1.22	12	"	21	178.1	67.8	90.5	86.5	5000
6.1.22	13	"	15	163.4	52.8	84.5	77.5	3240
11.1.22	14	"	16	187.2	65.0	96.8	83.0	4670
12.1.22	16	"	16	164.2	45.5	82.3	74.5	3370
1.6.22	17	"	34	187.0	77.7	95.7	94.0	5050
2.6.22	18	"	15	157.5	45.9	84.0	74.0	2940
4.5.22	19	"	32	185.7	68.8	96.2	89.5	5440
10.5.22	20	"	32	181.9	57.8	95.2	81.0	5080
12.5.22	21	"	21	173.6	62.5	93.1	85.0	4570
19.5.22	22	"	29	174.4	67.4	92.0	90.0	4480
16.5.22	23	"	26	177.4	69.5	94.3	89.0	4720
17.5.22	24	"	40	164.9	56.8	89.8	89.5	4010
23.5.22	25	"	25	173.5	78.5	90.2	97.5	4720
24.5.22	26	"	22	179.5	71.6	90.7	92.5	5310
26.5.22	27	"	38	174.6	78.9	93.0	99.5	5200
29.5.22	28	"	22	173.4	58.8	90.5	84.0	4290
30.5.22	29	"	31	168.0	61.15	87.7	90.0	4350
10.6.22	30	"	27	181.2	70.0	94.7	96.0	6830
29.7.22	31	"	13 $\frac{1}{2}$	149.6	34.8	77.0	65.5	2200
14.6.22	32	"	15	168.9	48.5	84.3	77.0	3200
20.6.22	33	"	27	183.0	59.1	98.2	80.8	5240
25.6.22	34	"	29 $\frac{1}{2}$	185.3	101.0	94.2	106.0	5450
30.6.22	36	"	25	176.0	53.21	93.5	81.5	4740
12.7.22	37	"	36	174.2	63.2	89.3	89.6	4530
18.7.22	38	"	27 $\frac{1}{2}$	173.4	69.0	91.2	89.5	3870
25.7.22	39	"	13 $\frac{1}{2}$	158.7	49.4	82.7	81.5	3550
30.7.22	40	"	15 $\frac{1}{2}$	162.7	47.0	84.9	78.0	3700
30.7.22	41	"	14 $\frac{1}{2}$	157.7	50.5	81.6	83.0	3420
1.8.22	42	"	12 $\frac{3}{4}$	152.3	38.7	78.6	70.0	3060
2.8.22	43	"	11 $\frac{1}{2}$	147.0	39.2	77.2	73.0	2760
3.8.22	44	"	15 $\frac{1}{2}$	156.2	46.8	80.1	79.0	3230
5.8.22	45	"	9 $\frac{1}{2}$	133.5	28.2	71.3	63.0	1940
19.8.22	46	"	13 $\frac{1}{2}$	144.9	35.0	78.2	71.5	2480
20.8.22	47	"	30	180.1	69.8	91.5	91.0	5360
23.8.22	48	"	16 $\frac{1}{2}$	171.2	54.5	89.0	79.5	4130
24.8.22	49	"	17	179.0	58.8	94.3	82.5	3880
25.8.22	50	"	15 $\frac{1}{2}$	151.6	38.6	77.6	73.0	3250
26.8.22	51	"	12 $\frac{1}{2}$	148.4	33.2	74.2	71.5	2800
16.11.21	1	"	23	177.0	55.4	89.8	86.0	4020
18.11.21	2	"	29	172.0	51.7	88.4	83.5	3850
12.12.21	9	"	19	178.2	66.5	93.1	88.0	4460
12.1.22	15	"	32	179.5	57.8	95.5	84.5	4610
28.6.22	35	"	35	174.1	65.7	88.9	87.0	4080

Actual measurements of the subjects examined.

Subjects rejected for reasons stated in the text.

APPENDIX II B.

Ser. No.	Date.	Lying Sys.	B. P. Di.	Ulb. Un. Time, a.m.	Lying Pulse-Rate Mean of 4 counts.	Consumption of O ₂ per 15 min. S. T. P.	R. Q.	Observed Calcs. per 24 hours.	Dreyer. Calc. $\frac{\text{Calcs.}}{\sqrt{W}}$ $C \times A^{0.1333}$	% Δ .	Benedict. Calc. Multi- ple Pr. Tables.	% Δ .	Du Bois. Sur- face Square Metres.	Calc. Calcs.	% Δ .	Body Temp. ° Fahr- renheit.
1	16.11.21	182	74	194 10.30	122.0	4436	0.820	2078	1644	+26.4	1558	+33.4	1.687	1599	+29.9	98.4°
2	18.11.21	128	75	193 10.45	106.0	4444	0.808	2052	1545	+24.8	1442	+31.7	1.605	1522	+28.1	98.0°
3	20.11.21	115	75	211 10.30	92.0	4559	0.843	2127	1545	+37.7	1442	+47.4	1.746	1655	+22.6	97.6°
4	23.11.21	116	70	190 10.35	73.0	4124	0.884	1942	1710	+25.7	1615	+34.8	1.494	1416	+7.2	97.6°
5	9.12.21	108	74	195 11.0	75.0	3739	0.916	1774	1486	+3.8	1365	+7.9	1.649	1563	+5.3	97.6°
6	23.12.21	120	72	205 11.30	78.0	3784	0.798	1741	1486	+1.9	1365	+8.1	1.786	1693	+5.0	98.0°
7	7.12.21	125	75	187 11.0	67.0	3153	0.863	1477	1486	+0.6	1365	+8.9	1.979	1876	+5.3	97.6°
8	22.5.22	133	80	187 11.5	61.0	3225	0.798	1486	1568	+16.2	1541	+12.1	1.786	1693	+2.1	97.8°
9	12.12.21	118	80	183 11.45	58.5	3716	0.836	1728	1568	+3.5	1757	+4.5	1.856	1759	+5.1	98.2°
10	16.12.21	123	70	195 10.50	67.0	4227	0.789	1917	1690	+13.4	1757	+9.0	1.856	1759	+8.9	98.2°
11	22.12.21	122	75	190 11.30	49.5	4285	0.775	1962	1690	+16.0	1757	+11.6	1.856	1759	+11.5	98.2°
12	2.1.22	128	85	192 10.45	61.0	3769	0.972	1813	1812	+0.1	1833	-1.0	1.924	1824	-0.6	97.6°
13	6.1.22	122	80	190 11.0	48.0	3821	0.908	1810	1812	+0.1	1833	-1.0	1.924	1824	-0.6	97.6°
14	11.1.22	118	74	186 10.45	44.0	4423	0.886	2084	1871	-0.1	1808	-1.2	1.911	1812	-0.8	97.8°
15	12.1.22	110	70	187 11.25	48.0	4117	0.950	1970	1678	+5.3	1748	+5.1	1.847	1751	+8.8	97.8°
16	12.1.22	120	74	197 11.25	59.0	3832	0.958	1838	1678	+9.4	1748	+10.9	1.847	1751	+4.9	97.8°
17	1.6.22	114	64	177 10.30	60.0	4004	1.000	1940	1543	+15.5	1508	+6.6	1.560	1722	+10.8	97.0°
18	6.1.22	112	76	174 11.5	64.0	3313	0.972	1600	1543	+3.7	1508	+6.9	1.881	1941	-7.1	98.0°
19	11.1.22	118	74	186 10.45	70.0	4386	0.895	2071	1785	+16.1	1787	+15.9	1.881	1941	+6.7	98.0°
20	12.1.22	110	72	181 11.20	69.0	4286	0.905	2028	1785	+13.7	1787	+13.5	1.881	1941	+4.5	98.0°
21	12.1.22	110	70	187 11.25	54.5	2951	0.854	1379	1625	-15.1	1543	-10.6	1.785	1645	-16.2	97.2°
22	12.1.22	104	68	182 12.5	58.5	2899	0.843	1351	1625	-16.9	1543	-12.3	1.785	1645	-17.8	97.2°
23	12.1.22	120	74	186 10.45	67.5	3066	0.755	1397	1464	-4.5	1406	-0.6	1.470	1517	-7.8	98.0°
24	1.6.22	114	70	184 11.30	66.0	3205	0.700	1442	1464	-1.4	1406	-2.6	1.470	1517	-4.9	98.0°
25	1.6.22	115	72	181 11.0	68.0	3377	0.800	1789	1743	+2.4	1841	+2.98	2.027	1922	-7.08	97.1°
26	1.6.22	112	68	186 11.30	68.0	3922	0.715	1768	1743	+1.4	1841	-3.97	2.027	1922	-8.01	97.1°

Respiration too slow and irregular to measure volume.

18	2.6.22	115	68	184	11.40	71.5	3792	0.744	1723	1492	+ 15.5	1385	+ 24.4	1.431	1580	+ 9.1	97.0°
19	4.5.22	120	80	172	10.45	60.5	3652	0.700	1643	1708	+ 10.1	1726	+ 18.6	1.915	1815	+ 4.0	98.2°
20	8.5.22	112	76	182	11.15	48.5	3270	1.000	1584	1594	+ 0.6	1555	+ 10.4	1.752	1661	+ 5.0	98.2°
21	12.5.22	110	76	178	11.45	46.5	3179	1.000	1540	1700	- 3.3	1653	+ 0.9	1.751	1660	- 7.2	97.8°
22	12.5.22	140	86	188	11.15	63	3524	0.932	1679	1700	+ 1.2	1653	+ 1.5	1.751	1660	+ 0.9	97.8°
22	19.5.22	122	80	186	11.45	62.5	3813	0.795	1755	1675	+ 3.3	1670	+ 6.1	1.814	1720	+ 1.1	97.5°
22	19.5.22	122	80	196	11.0	75.5	3999	0.763	1826	1675	+ 8.9	1670	+ 9.3	1.814	1720	+ 6.0	97.5°
22	19.5.22	120	78	183	12.0	74	4113	0.718	1855	1675	+ 10.7	1670	+ 11.0	1.814	1720	+ 7.8	97.5°
23	16.5.22	124	84	190	11.10	58	3516	1.000	1704	1721	- 1.0	1734	- 1.7	1.861	1764	- 3.4	97.8°
24	17.5.22	125	82	194	11.30	60	3599	1.000	1744	1520	+ 1.4	1403	+ 0.6	1.620	1497	- 1.1	97.8°
24	17.5.22	136	84	194	11.0	62.5	3324	0.716	1589	1520	+ 4.5	1403	+ 13.3	1.620	1497	+ 6.0	97.4°
25	23.5.22	130	80	191	11.45	62.5	3219	0.860	1506	1790	- 1.0	1845	+ 7.3	1.923	1828	+ 0.4	97.7°
25	23.5.22	98	54	179	11.20	70.5	4098	0.820	1398	1790	+ 6.0	1845	+ 2.9	1.923	1828	+ 3.8	97.7°
25	23.5.22	126	72	179	11.45	65	4098	0.837	1906	1790	+ 6.5	1845	+ 3.3	1.923	1828	+ 4.2	97.7°
26	24.5.22	130	86	171	10.55	52	3945	0.804	1820	1756	+ 3.6	1800	+ 1.11	1.901	1802	+ 1.1	97.0°
26	24.5.22	126	78	170	11.25	51	3729	0.786	1713	1756	- 2.4	1800	+ 1.11	1.901	1802	+ 4.7	97.0°
27	26.5.22	128	88	186	11.0	50	3705	0.820	1716	1757	- 2.9	1767	- 4.83	1.941	1840	- 6.7	97.2°
27	26.5.22	126	80	186	11.0	50	3636	0.820	1684	1757	- 4.15	1767	- 4.7	1.941	1840	- 8.5	97.2°
28	29.5.22	127	76	190	11.40	72	3553	0.820	1646	1639	+ 0.5	1594	+ 3.3	1.705	1616	+ 1.9	—
29	30.5.22	122	65	183	12.5	68	3521	0.820	1631	1603	- 0.4	1539	+ 2.3	1.694	1606	+ 0.9	97.0°
29	30.5.22	124	78	198	10.10	62	3348	0.806	1545	1603	- 3.6	1539	- 0.3	1.694	1606	- 3.8	97.0°
30	10.6.22	122	80	188	10.30	58.5	3339	0.839	1619	1811	+ 1.0	1751	+ 5.2	1.895	1796	+ 0.8	97.8°
30	10.6.22	126	80	190	11.0	77.5	3775	0.971	1816	1811	+ 0.3	1751	+ 3.7	1.895	1796	+ 1.1	97.8°
31	29.7.22	127	88	178	11.25	79.0	4007	0.874	1882	1815	+ 3.9	1751	+ 7.5	1.895	1796	+ 4.5	98.4°
31	29.7.22	132	80	176	10.30	84	3053	0.820	1414	1815	+ 6.25	1202	+ 17.65	1.225	1352	+ 4.4	98.4°
32	14.6.22	122	78	193	11.0	80	2931	0.820	1358	1586	+ 13.0	1477	+ 17.5	1.541	1701	+ 0.3	97.8°
32	14.6.22	140	82	184	11.20	75	3752	0.815	1736	1586	+ 13.0	1477	+ 17.5	1.541	1701	+ 2.1	97.8°
32	14.6.22	145	80	184	11.20	72	3665	1.000	1776	1586	+ 15.6	1477	+ 20.2	1.541	1701	+ 4.4	97.8°
33	20.6.22	135	95	188	11.5	77	3739	0.967	1797	1675	+ 16.9	1612	+ 21.7	1.777	1685	+ 5.6	97.6°
33	20.6.22	135	95	188	11.5	57	3665	0.705	1651	1675	- 1.5	1612	+ 2.4	1.777	1685	- 2.0	97.6°
34	25.6.22	185	95	188	11.40	61	3676	0.820	1703	1931	+ 1.7	2185	+ 5.6	2.251	2134	+ 1.1	97.0°
34	25.6.22	107	70	181	11.30	59.5	4511	0.870	2216	1931	+ 9.6	2185	+ 3.16	2.251	2134	+ 0.94	97.0°
34	25.6.22	107	70	186	12.0	60.5	4657	0.870	2276	1931	+ 17.9	2185	+ 4.2	2.251	2134	+ 6.7	97.0°
35	28.6.22			188	11.15	noon		0.820	1763	1550	+ 13.7	1605	+ 9.8	1.792	1699	+ 3.77	97.8°
35	28.6.22			188	11.15	64	3801	0.820	1763	1550	+ 13.7	1605	+ 9.8	1.792	1699	+ 3.77	97.8°
36	30.6.22	140	98	186	11.45	61	3992	0.820	1849	1609	+ 18.9	1510	+ 15.2	1.652	1566	+ 8.83	97.8°
36	30.6.22	115	80	198	11.0	70	3487	0.943	1666	1609	+ 3.6	1510	+ 10.3	1.652	1566	+ 6.4	97.8°
36	30.6.22	105	75	190	11.30	61.5	3395	0.866	1586	1609	- 1.5	1510	+ 5.0	1.652	1566	+ 1.3	97.8°

APPENDIX II B (continued).

Ser.	Date.	Lying Sys.	Lying B.P. Di.	Hb. Un. Time, a.m.	Lying Pulse-Rate Mean of 4 counts.	Consumption of O ₂ per 15 min. S. T. P.	R. Q.	Observed Cals. per 24 hours.	Dreyer. Cals. \sqrt{W} $C \times A^{0.733}$	% Δ .	Benedict. Cals. Multi- ple Pr. Tables.	% Δ .	Du Bois. Sur- face Square Metres.	Calc. Cals.	% Δ .	Body Temp. ° Fah- renheit.
37	12.7.22	120	85	174 10.40	66	3769	0.800	1737	1593	+ 9.4	1563	+ 11.1	1.764	1672	+ 3.9	96.8°
		116	78	171 11.15	60	3746	0.800	1727		+ 8.7		+ 10.5			+ 3.3	
38	18.7.22	136	86	190 11.0	67.5	3755	0.820	1739	1673	+ 3.9	1700	+ 2.3	1.825	1730	+ 0.52	98.0°
		128	80	190 11.30	65.5	3789	0.820	1755		+ 4.9		+ 3.2			+ 1.45	
39	25.7.22	130	72	194 16.0	52.5	3085	0.820	1406	1588	- 10.73	1349	+ 4.23	1.485	1639	+ 14.22	97.6°
		134	84	188 10.20	51.5	3088	0.820	1430				+ 6.00			- 12.75	
40	30.7.22			176 10.15	56	2920	0.820	1333	1545	- 10.96	1239	+ 9.2	1.480	1634	- 17.2	97.8°
		108	60	181 10.45	54	3014	0.820	1396				+ 12.67			- 16.57	
41	30.7.22			174 11.15	58.5	3239	0.820	1500	1589	- 6.19	1455	+ 3.09	1.492	1647	- 8.93	97.4°
				176 11.45	59	3199	0.820	1482				+ 1.86			- 10.01	
42	1.8.22			170 10.15	61.5	3340	0.820	1547	1400	+ 10.45	1280	+ 20.86				98.4°
		112	70	171 10.45	63.5	3356	0.820	1554				+ 21.41				
43	2.8.22			176 9.50	74	3177	0.820	1472	1428	+ 1.30	1267	+ 12.23				98.2°
		128	80	183 10.20	66.5	3071	0.820	1422				+ 13.17				
44	3.8.22			177 9.40	65.5	3396	0.820	1573	1500	+ 4.75	1390	+ 12.81	1.434	1583	- 0.63	97.3°
		118	66	181 10.10	67.5	3385	0.820	1568				+ 18.04			- 0.95	
45	5.8.22			172 9.30	68.5	2848	0.820	1319	1249	+ 4.10	1070	+ 23.27				98.7°
		100	64	172 10.0	64.5	2727	0.820	1263				+ 6.42				
46	19.8.22			172 9.30	69.5	2757	0.820	1277	1389	- 7.05	1200	+ 10.25	1.201	1326	- 3.70	98.4°
		128	78	172 10.0	65.5	2856	0.820	1323				- 7.51			- 0.23	
47	20.8.22			183 10.40	61	3429	0.820	1588	1675	- 5.14	1717	- 5.65	1.885	1787	- 11.14	97.4°
		112	72	190 11.20	57.5	3497	0.820	1620		- 3.24		- 2.44			- 9.35	
48	23.8.22			181 9.30	62.5	3284	0.820	1521	1619	- 5.41	1559	- 1.15	1.635	1687	- 9.84	98.0°
		110	70	188 10.10	57.0	3326	0.820	1541				+ 1.15			- 8.65	
49	24.8.22			181 9.20	69	3617	0.820	1675	1719	- 2.68	1656	+ 0.91	1.745	1801	- 7.0	96.8°
		120	78	183 10.0	63.5	3608	0.820	1671				+ 21.57			- 7.22	
50	25.8.22			190 9.30	81.5	3347	0.820	1550	1384	+ 12.90	1275	+ 23.61	1.293	1427	+ 8.62	98.4°
		116	76	183 10.0	82	3402	0.820	1576				+ 15.51			+ 10.44	
51	26.8.22				77	2942	0.820	1363	1351	+ 0.89	1180					

APPENDIX III.

1. Dreyer's method of estimating haemoglobin as compared with the Haldane standard shows:

Dreyer 192 Hb. units = 100 per cent. Haldane.

N.B.—I am indebted to Professor Dreyer for the above figure, which he had determined.

2. By the Haldane standard the haemoglobin-age groups of Table V show—

Age.	No.	Dreyer Units.	Haldane Hb %.
15 years	7	176.5	91.9
15-20 "	10	182.8	95.2
20-25 "	10	190.2	99.1
25-30 "	9	185.6	96.7
30-40 "	9	185.6	96.7

3. The highest and lowest values found in this series are—

No. 3	211 Dreyer units	109.9 per cent. Haldane.
Nos. 26 and 42	171 Dreyer units	89.1 per cent. Haldane.

CRITICAL REVIEW

JAUNDICE: A REVIEW OF RECENT WORK

By J. W. McNEE

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Introduction.

THERE must be few sections of medicine around which a larger literature has grown up than the pathology of different forms of jaundice. In recent years there has been a great revival of interest in the subject, following a long lull in active research during which what are often termed the 'classical theories' of jaundice held uncertain sway. These theories are briefly referred to later on in the text to show how greatly they have now required modification and alteration. Some can be discarded altogether in the light of newly-discovered facts. The new information at our disposal has come chiefly from experimental and clinical work carried out in America, France, Germany, and Holland. In our own country comparatively little work has been done, and this is reflected in a perusal of recent British text-books of medicine, where, as a rule, no attempt is made to bring the subject into line with the new beliefs. A well-known description of all appertaining to jaundice is contained in Rolleston's text-book of hepatic diseases, published in 1912, but nearly all the important work dealt with in the present review has been published since then.

The chief series of observations which have had an important bearing on the recent developments may be grouped, for clearness, under separate headings. The observations are, however, so frequently welded together and interdependent, that discussion under such grouping is only partly possible.

The recent important advances in the study of jaundice are the following:

1. The work from Aschoff's school in Freiburg-im-Breisgau, which has dealt particularly with the haemolytic forms of jaundice, and with the relations both to general and hepatic pathology of the so-called 'reticulo-endothelial system' of cells.

2. The work of American authors in Philadelphia and Baltimore, among whom Pearce, Austin, Krumbhaar, Eisenbrey, and Whipple, Hooper, and King may be named. These experiments have dealt chiefly with the interrelationships of the spleen and liver to blood destruction and haemolytic jaundice, and with the sites and method of formation of bile pigment.

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More recently Eppinger and others in Germany have pursued experimental and clinical work along very similar lines, amplifying their observations, however, by making use of the facts now known concerning the reticulo-endothelial system, and by employing the methods of van den Bergh described below.

3. The work of the French school, in which the names of Brulé, Chauffard, Gilbert, and Widal figure prominently. All the important observations are summarized in Brulé's monograph on jaundice, and nowhere is the isolation and independence of French research work more obvious than in relation to this subject. The new observations concerning jaundice, as we understand the term, are difficult to sift out, since the investigations cover the whole field of hepatic insufficiency and its results, retention of bile pigment being dealt with as an important but inconstant incident. Theories of bilirubin and urobilin metabolism, alterations in the bile acids, and of cholesterol, are all linked up with other disturbances of hepatic function. New methods of French origin, such as Widal's 'haemoclastic crisis', are considered in relation to jaundice and diseases of the liver generally. Two important new conceptions, for which the credit is essentially French, may be noticed here:

(a) The recognition of so-called 'dissociated jaundice'. The essence of this observation, which is dealt with at length later on, is that bile acids or bile pigments may be retained singly and separately in hepatic disease. It is obvious that, in the strict sense of the term, jaundice can only occur in pigmentary retention.

(b) The conception of functional derangement of the glandular cells of the liver leading to hepatic insufficiency and to jaundice.

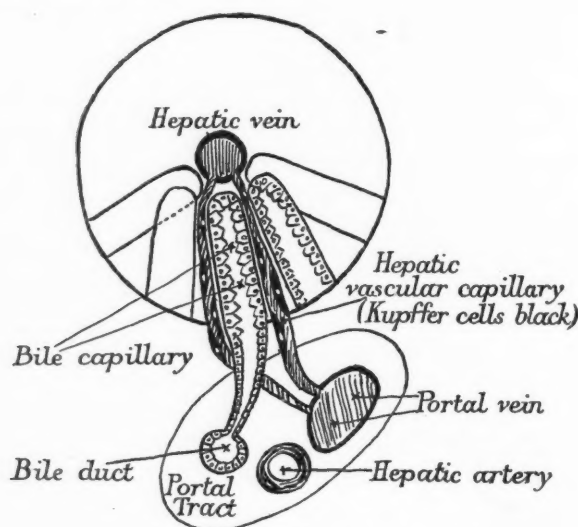
4. The most recent and probably the most important work of all is due to Hijmans van den Bergh, formerly of Groningen, now of Utrecht. This writer more than any one else has transferred our outlook on jaundice away from the colour of the skin and presence or absence of bile pigment in the urine and faeces, to the changes occurring in the blood-serum. He has done this by his success with a method of detecting bilirubin in blood-serum which is more accurate and delicate than any test previously employed for this purpose in clinical or experimental work.

Many new facts have been elicited as a result of the application of this method by van den Bergh and others following him. The most important observation of all is that by this test two different and distinguishable forms of bilirubin can be recognized in the blood-serum in cases of jaundice. In the one case the bilirubin gives an immediate colour reaction with the reagents employed. In the other, the colour reaction only appears after a more or less prolonged interval, and frequently not at all. By this method there has been opened up an entirely new way of approach in the study of the pathology of clinical forms of jaundice.

A New Theory of Jaundice.

Out of all these recent observations has been built up a new theory of jaundice which fits the clinical facts in a way which none of the views hitherto held have even approached. This theory, which has received widespread support, at least forms a rational basis for clinical teaching at present, and for research work in the future. It is so often referred to, either directly or by implication, in the course of this review that it seems best to give its essentials at once, even before the steps by which it has been built up are considered under various headings.

Before doing so, however, it is necessary to refer for a moment to the finer histological structure of the liver lobule and its relations to the biliary tract. It is interesting to find how much we owe for our knowledge of the microscopic anatomy of the liver to the work of Lionel S. Beale, of King's College Hospital, carried out between 1850 and 1860.



The present writer has come to regard the structure of the liver in the following way. Each lobule can be considered schematically as made up of a series of radiating tubular glands, shaped like a test-tube, with the closed end pointing to the centre of the lobule. The polygonal glandular cells lie, as it were, along the wall of the test-tube, which may be taken to represent a basement membrane. In the centre of the test-tube, surrounded entirely by the polygonal cells, lies the bile capillary. Reference to the diagram above illustrates this description, and it will be seen that the bile capillary begins, near the bottom of the 'test-tube', at a blind end.

Between the tubular glands run the wide portal vascular capillaries, passing from the portal tract to join the branch of the hepatic vein in the centre of the lobule. Along the walls of these capillaries lie a number of large endothelial

cells (Kupffer cells) which form an important part of Aschoff's 'reticulo-endothelial system'. These cells of von Kupffer are very abundant in birds and some animals, but are less numerous in man.

The theory of jaundice developed as a result of the recent investigations has at its root the view that the polygonal glandular cells of the liver are not essentially concerned with the manufacture of bile pigment, but have chiefly to do with its transference from the vascular capillaries into the bile capillaries. It seems probable, if this view be correct, that in passing through the polygonal cells bilirubin is modified in some way and this is the explanation offered at present to account for the two varieties of bilirubin made evident by the van den Bergh test. The view is further put forward that it is the cells of the reticulo-endothelial system, either those in the spleen or the Kupffer cells of the liver, which deal with the breaking down of haemoglobin and the elaboration of bile pigment. This conception is based entirely on animal experiments, in which, during blood destruction, bile pigment, haemosiderin, and fragmented red corpuscles have been seen together in the endothelial cells of the liver. No one has ever seen haemoglobin being changed into bile pigment within the glandular cells of the liver, nor indeed has any one ever seen bile pigment in the polygonal cells at all in *healthy* human or animal livers.

The chief difficulty in accepting the theory put forward lies at present in the impossibility of correlating what happens under definitely pathological circumstances with what may happen in health.

Taking, however, this theoretical view, that it is the cells of the reticulo-endothelial system (including the Kupffer cells of the liver) which are concerned with the elaboration of bilirubin, then jaundice might arise in a variety of ways.

1. Where the bile pigment, formed in the endothelial cells, passes through the glandular cells to reach the bile capillaries, but is obstructed in its outflow there, becoming finally reabsorbed into the blood by methods which are discussed later.

2. Where, owing to damage and functional derangement of the polygonal cells, the bile pigment from the endothelial cells is unable to enter them. It must pass instead directly into the hepatic vein, and so accumulate in the general circulation.

A second variety of jaundice arising in a closely similar way might occur where, in excessive blood destruction, more bilirubin is formed by the reticulo-endothelial system than the polygonal liver-cells can deal with. Under such circumstances some bile pigment might pass normally through the glandular cells into the bile passages, the excess going directly into the hepatic vein.

3. Where, in addition to damage of the polygonal cells, there is obstruction in the bile passages. Under such circumstances some bilirubin might pass directly into the hepatic vein, and some pass through polygonal cells, which are still functioning, to be obstructed in the bile passages and reabsorbed.

Such a view would satisfactorily explain the presence together of both of van den Bergh's varieties of bilirubin in the serum in some cases of jaundice.

Although jaundice, in the strict sense of the term, depends entirely on disturbances in the metabolism of bile pigment, it is manifestly impossible, as the French writings well show, to ignore disturbances in the other important constituents of the bile. The effects of the bile acids, and even of cholesterol, are recognizable in various ways in the clinical study of jaundice, although they may be invisible to the eye.

A considerable amount of information is now available with regard to the metabolism of cholesterol, although in incomplete form. Little of importance has emerged since a review on the subject was published by the writer in this Journal in 1913.

The present position of our knowledge of the bile acids in jaundice, and even in health, is summarized by Whipple with telling effect in the following words: 'If our ignorance about the complete story of the bile pigments is disturbing, then our lack of understanding as to the source and internal metabolism of the bile acids is pathetic—this in spite of much careful study and investigation.'

It is, of course, beyond the scope of a review on jaundice to deal with work concerning interference with other hepatic functions which are known to us, although incidental reference is necessary to some of the results obtained in cases where jaundice exists.

The Classical Theories of Jaundice.

The older views are still to be found in many of the recent text-books, but for a first-hand classical account of them reference may be made to three publications, appearing at different dates. These are, first, the monograph of Stadelmann, *Der Icterus und seine verschiedenen Formen*, Stuttgart, 1891; second, the review 'Der Ikterus', written by Eppinger, *Ergebnisse der innern Medizin und Kinderheilkunde*, 1908; and third, the chapter on jaundice in Rolleston's *Diseases of the Liver, Gall-bladder, and Bile Ducts* (1912).

These older conceptions are dealt with in greater detail under special sections of this review, but, summarizing them broadly, it may be said that, beginning in the time of Virchow with the possibility that jaundice might be either hepatogenous or anhepatogenous in origin, the view gradually narrowed down. The anhepatogenous form was excluded after the experiments of Minkowski and Naunyn (1886), and it became affirmed that all jaundice was hepatogenous and arose only in the liver. Further, it gradually became accepted, chiefly as a result of Eppinger's work (1908), that all forms of icterus were essentially obstructive, whether the hindrance occurred in the larger bile ducts or in the finest bile capillaries. This view has now been retracted by Eppinger himself.

In Rolleston's book (1912) doubts were beginning to appear regarding the conceptions named above, and on page 533 he writes, 'on the other hand, opinion is now inclining to the view that jaundice may in certain conditions be independent of any obstruction in the biliary apparatus and truly haemolytic in origin'.

It will be seen in the present account of jaundice how the first of the classical theories, put forward by Virchow from his observations on haematoidin, is now resuming its old supremacy, although based on an entirely different type of research work.

The 'Reticulo-endothelial System' and its Relations to the Metabolism of Bile Pigment.

The 'reticulo-endothelial system' is a term introduced into medical terminology by Aschoff, and is in current use on the Continent (Aschoff, Jaffé). It is a convenient term to employ when describing the activities of a system of endothelial cells widely scattered throughout the body, but having a more highly specialized function in some situations. Some such term is necessary to describe what is really, in a way, an organ of the body, although distributed almost as widely as the lymphoid tissues. The cells included in the system are best identified by a brief description of the development of the conception of the reticulo-endothelial system. This began with the work of Ribbert (1904), who described the results of intravenous injection of carmine into living animals. Ribbert observed that certain cells of the body, such as the Kupffer cells of the liver, the endothelial cells of the spleen, bone-marrow, and lymphatic glands, the interstitial cells of the testes, the reticular cells of the thymus, and the capillary endothelium of the suprarenals, all retained the dye, whereas other endothelial cells, such as the ordinary capillary endothelium of blood-vessels, remained free. Ribbert gave the name 'pyrrhol cells' to the group which contained the carmine, and suggested that they might be important sources of internal secretions and of metabolic activity. The study of these cells has been greatly developed by Aschoff and his pupils, especially Kiyono, and the latter has published an important monograph on the subject. Other work has shown the importance of the reticulo-endothelial system in the metabolism of fats, especially lipid fats (Landau and McNee), but for the present review the influence of this system on the metabolism of haemoglobin and its derivatives is alone important (Aschoff). The activities of the reticulo-endothelial system in this connexion have been chiefly studied under conditions in which there has been excessive blood destruction, and there is still room for investigation of what happens under normal as apart from such pathological circumstances. In excessive blood destruction, both in man and animals, there is no doubt that the cells of this system take up, by phagocytosis, intact red corpuscles, debris of corpuscles, and even free haemoglobin dissolved in the serum. In these cells haemoglobin is broken down, and the iron-containing portion of the molecule (haemosiderin) can readily be demonstrated in them by the Prussian blue reaction. The problem whether bilirubin is actually formed within these cells, or only a precursor of it, is not yet solved for human pathology, although it would be of critical importance to do so. It is certain that the cells of this system in different organs of the body do not act with equal intensity as regards the breaking down of haemoglobin, and this

raises the question, already referred to, of specialized functional activity of parts of the system. There is no doubt that in man and the higher animals the endothelial cells of the spleen play the preponderating rôle in the breaking down of haemoglobin, and the activity of the spleen in this way is quite obvious histologically even in health. It seems probable, chiefly from the experimental observations of Lepehne and the writer, that in excessive blood destruction other parts of the system may be thrown into activity to help the spleen. It must be remembered, however, in interpreting all the experimental work on this subject, that the cells of the reticulo-endothelial system are not evenly distributed in different animals. In birds, for example, the cells of this system are in enormous numbers in the liver (Kupffer cells), whereas the spleen as an organ is extremely small. In man the Kupffer cells in the liver are relatively few, while the spleen is large and highly developed.

The importance of all this work on the reticulo-endothelial system is especially in connexion with the type of jaundice called 'haemolytic jaundice', although it is also partly involved, in the writer's opinion and that of many others, in the mechanism of 'toxic and infective jaundice'.

*Bilirubin in the Blood-serum (Bilirubinaemia) in the Light of the
Observations of Hijmans van den Bergh and others.*

This investigation of this fundamental aspect of jaundice has already yielded a mass of information of great importance, especially in regard to the theory of jaundice which has been put forward as a working hypothesis in the introductory section.

The first important paper was published in 1913 (Hijmans van den Bergh and Snapper), but later the whole of the available information was collected by van den Bergh in a monograph, *Der Gallenfarbstoff im Blute*, published in 1918. Since that time numerous other writers, especially in Germany, have developed the subject along the lines laid down in this monograph.

Hijmans van den Bergh begins his monograph by stating that in the study of icterus far too much attention has been paid in the past to the coloration of the skin and mucous membranes, and to the presence or absence of bile in the urine and faeces. He deals with the difficulties and fallacies arising from such observations, and makes his first main point, namely, that icterus essentially depends on an increase in bile pigment in the serum. This, of course, shows a similar trend of thought to that which in recent times has been brought into the study of diseases like diabetes mellitus and nephritis.

Thinking in this way, van den Bergh was met with the difficulty of finding a suitable qualitative and quantitative test for bilirubin in an albuminous fluid such as blood-serum. He investigated many methods which had been employed for this purpose, but found none of them satisfactory or practical for clinical purposes until he virtually rediscovered the colour reaction given by bilirubin with the diazo reagent of Ehrlich. An attempt is evident in recent German

papers to claim the test now applied to the serum in jaundice under the name of the Ehrlich-Pröschner reaction. There seems no doubt, however, that since van den Bergh first applied the reaction to the examination of blood-serum, and has made such important original observations and deductions from its use, the test as applied to the study of jaundice should with fairness and right be known as the 'van den Bergh test'.

The actual history of the diazo reaction is briefly as follows: Ehrlich (1883-4) discovered that if a small amount of a diazonium salt in acid solution be added to an alcoholic solution of bilirubin, coupling occurred with the development of an azo-dye, 'azo-bilirubin'. This dye was isolated and investigated both chemically and spectroscopically by Pröschner (1900), who pointed out even then that this apparently excellent reaction for bilirubin had not been made use of in clinical work. Thereafter the method appears to have been forgotten, until the advent of van den Bergh, who found that this reaction solved his difficulties and gave him an accurate test for *small* amounts of bilirubin in *small* amounts of serum. With regard to the delicacy of the test, he found that a solution of 1 in 1,500,000 of pure bilirubin dissolved in alcohol still gives a positive result. Biliverdin, and other yellow substances which may rarely be present in human serum and at first sight imitate bilirubin, do not give the reaction. Next, van den Bergh made the original and important observation that in some cases of jaundice it is unnecessary to bring the bilirubin into alcoholic solution, but that a positive coupling, with production of the azo-dye, can be obtained by adding the diazo reagent direct to the icteric serum.

In this way he was able at once to divide icteric sera into two groups:

1. Sera giving a colour reaction at once (maximal within 30 seconds) on the addition of diazo reagent directly to the serum—van den Bergh's *prompt (or immediate) direct reaction*.

2. Sera giving no colour reaction, or only after long delay, on the addition of diazo reagent direct to the serum—van den Bergh's *delayed direct reaction*.

Every icteric serum gives an immediate colour reaction with the diazo reagent after precipitation with alcohol so as to bring the bile into alcoholic solution. The application of the method to this alcoholic solution of bilirubin, derived from the serum, is known as *van den Bergh's indirect reaction*. Full details of the actual technique, and quantities of serum required, are given in an appendix.

It emerged from the examination of many sera that in complete obstructive jaundice a prompt direct reaction is always obtained, whereas in sera from cases of haemolytic jaundice, in the normal yellow serum of the horse, and in the serous fluid obtained from haemorrhagic effusions in the chest or abdomen, the direct reaction is always negative, or at least of the delayed type. Thus van den Bergh, in his monograph (1918), was able to put forward the view, founded on the new theory of jaundice already mentioned, that the occurrence of a prompt direct reaction might mean the presence of bilirubin which has passed through the polygonal cells of the liver, and then been absorbed on account of obstruction;

while in the case of sera giving the delayed reaction only he has suggested that the bilirubin has been formed independently of the liver-cells and has not passed through them.

This very important explanation suggested for the occurrence of two types of bilirubin in jaundice is strongly supported by two clinical facts :

1. Bile from the gall-bladder, which has, of course, passed through the liver, always gives a typical prompt direct reaction.

2. Bilirubin obtained in the serous fluid from haemorrhagic effusions in the chest or abdomen gives the delayed reaction only, or generally none at all. Such bile pigment has been made independently of the glandular cells of the liver.

Van den Bergh also found that icteric sera differed in other less important ways. He noticed that in sera giving a prompt direct reaction far more pigment is absorbed into the precipitate on the addition of alcohol for the indirect reaction than is the case in sera giving a delayed direct reaction. He noted also that the bilirubin in sera giving the prompt direct reaction is more readily oxidizable to biliverdin than is the other variety of the pigment.

For van den Bergh's method of applying the reaction to the quantitative estimation of bilirubin in the blood-serum the appendix should be consulted.

There is, so far, no uniformity in the terminology applied by writers subsequent to van den Bergh to the varying results of the test, especially in publications where quantitative estimations are not considered.

Feigl and Querner have drawn attention to an important variation in the result of the van den Bergh test, which requires an additional nomenclature, namely, the occurrence of *biphasic reactions* with the direct test, that is, on the addition of diazo reagent direct to the serum. Three kinds of result may thus be met with in the direct reaction :

1. A prompt reaction.
2. A delayed or negative reaction.
3. A biphasic result.

In sera giving a biphasic result a slight prompt coloration occurs at once, followed after a variable delay by gradual deepening of the colour reaction.

The occurrence of biphasic reactions can best be accounted for on the view that both the variety of bilirubin which gives the prompt reaction, and that which gives the delayed reaction only, are present in the serum together. In clinical work it is already recognizable that biphasic reactions can be subdivided further into *biphasic prompt* and *biphasic delayed* reactions, according as, on the view just stated, one or other variety of bilirubin predominates. The occurrence of biphasic reactions appears to be of especial interest in relation to the type of icterus discussed under the heading of 'Toxic and Infective Hepatic Jaundice'.

Great curiosity has naturally been aroused as to wherein the physical or chemical difference lies between bilirubin giving the prompt direct reaction and that giving a delayed reaction only or none at all.

It may be stated at once that this problem is not solved, although the views put forward are interesting and suggestive. Van den Bergh supposes that the

difference must depend either on some small alteration in the chemical constitution of the bilirubin molecule, or that in the case of the delayed reaction the bilirubin may be united to some albuminous substance in the serum, and this union must first be broken down (i. e. by alcoholic precipitation of the serum) before the colour reaction can appear.

Feigl and Querner have advanced the theoretical view of masking of bilirubin by lipoids. Lepelne has also investigated the problem and established the definite fact that, besides ethyl alcohol and methyl alcohol, only the addition of acetone can bring about a prompt reaction in all icteric sera. Ether, chloroform, zylol, amyl alcohol, and carbon bisulphide are all without effect. Thannhauser and Andersen have suggested that in cases giving the delayed reaction only, the pigment in the serum may not be bilirubin at all. But if this were true, it would be in the face of all the observations made in haemolytic jaundice with the Gmelin, Huppert, and Hammersten reactions, which all give typical results when sufficient serum is employed for adequately carrying out the test.

The Varieties of Jaundice.

Having considered from a general standpoint the recent work of Hijmans van den Bergh, and the recognition of the activities of the reticulo-endothelial system in blood destruction and bile-pigment metabolism, the classification of jaundice may now be considered in relation to the above developments, in relation to modern clinical observations and theories of icterus, and in relation to the older classical views. The old classification into hepatogenous and anhepatogenous, although in a measure correct, is no longer sufficient, nor is the division into obstructive and non-obstructive jaundice.

A simple and comprehensive classification which the writer considers to be the most satisfactory for teaching purposes in clinical medicine is into :

1. Obstructive hepatic jaundice.
2. Toxic and infective hepatic jaundice.
3. Haemolytic jaundice.

In the light of all recent work, including that of van den Bergh, Aschoff, and their pupils, all cases of icterus can be satisfactorily included under the above three divisions. It is, of course, certain that not all varieties of clinical jaundice can be confined absolutely to a single division. Toxic jaundice, with varying degrees of damage to liver-cells, may, for example, be combined with haemolysis, and in its later stages with obstruction in the biliary passages as well. Cases which fit clearly into one division only are, however, commonly met with.

Van den Bergh introduced, and has been copied by German writers, a classification into :

1. Mechanical jaundice.
2. Dynamic jaundice.

He groups as mechanical all forms depending on obstruction in the biliary passages, while every other variety is classified as dynamic. This classification

is, of course, built upon the theory used to explain the two varieties of bilirubin discovered by van den Bergh. In mechanical jaundice a prompt direct reaction is obtained, as in gall-bladder bile, and this is taken to mean that the bilirubin has passed through the liver-cells before being obstructed in its exit. In dynamic jaundice a delayed reaction occurs, which is taken to indicate that the bilirubin has not passed through the liver-cells. It is obvious that on this view the occurrence of a biphasic reaction might be taken to mean a combination of mechanical and dynamic icterus.

It is evident that such a classification is unsuitable, at present, for everyday use in clinical medicine.

Obstructive Hepatic Jaundice.

This variety arises in the liver by obstruction, either temporary or permanent, gradual or sudden, of the bile passages. It presupposes in its true form normal bile formation, and normal excretion through healthy liver-cells, at the onset of obstruction. This simple picture may not be fulfilled entirely, since the liver may be already damaged before obstruction occurs. This question is dealt with under the next section. Moreover, there is reason to believe that after obstruction has occurred a normal bile is no longer secreted, either as regards its bile acid constituents or its pigmentary fraction.

In jaundice following complete obstruction to the bile passages, as seen for example in cases of impacted calculus or neoplasm in the common bile duct, there is no doubt as to the main mechanism by which icterus arises, but there is still great doubt concerning the finer details.

The solution of the problem might be thought to be very readily amenable to experimental investigation by tying the common bile duct in animals, and indeed this type of experiment has been carried out by investigators too numerous to mention.

Some writers (Minkowski, Eppinger, Browicz, Sterling) have concluded that the mechanical factor plays only an incomplete part, and it is certain that different animals, even of the same species, behave in very variable fashion after such experimental obstruction. This is, without doubt, the reason for the diversity of opinion arising from such experiments. An important modern contribution to the subject of obstructive jaundice is that of Whipple and King (1911), who summarize the facts at issue, and discuss the two views which have been held concerning the escape of bile from the liver into the systemic circulation:

1. By way of the lymphatics.
2. By way of the hepatic vascular capillaries.

A series of experiments was carried out in large female dogs, the common bile duct being tied and divided, and lymph collected from a thoracic duct fistula. The urine, obtained by catheter, and the lymph from the fistula were examined for bile by the Salkowski test. The conclusion was arrived at from

these experiments that in obstructive jaundice the bile is absorbed by the hepatic vascular capillaries into the blood, and that the presence of a thoracic duct fistula in no way influences the development of icterus after tying the common bile duct. It was found, in a few experiments only, that sufficient bile pigment might appear in the lymph drained from the thoracic duct to give a positive reaction to the Salkowski test, but Whipple and King considered that this probably depended on the rapidity of bile secretion and on the amount of lymph flow.

Ogata (1913), in a research on obstructive jaundice, could find no relationship between the occurrence of jaundice and the presence of visible breaks in the walls of the bile capillaries. He lays special stress on the early occurrence of necrosis of liver-cells where the outflow of bile is obstructed.

With the arrival of the van den Bergh technique, by which the changes in the blood-serum, rather than those in the urine and lymph, could be followed, it was inevitable that the mechanism of obstructive jaundice should be investigated anew. Lepehne (1921) has published a small series of experiments in rabbits, but owing to the difficulties of obtaining experimental animals in Germany the work was perforce curtailed, and requires repetition. Five rabbits were used, the common bile duct being tied in every case, and the blood-serum thereafter investigated by the van den Bergh test. Normal rabbit's serum contains a mere trace of bilirubin. In three animals an increase of bilirubin in the blood—4 to 6.5 units—was recognizable within twenty-four hours. In one animal the reaction was biphasic prompt; in the two others a prompt direct reaction was obtained. In a fourth rabbit no increase in the bilirubin content of the serum was evident after forty-two hours, and yet a laparotomy on the following morning showed the presence of intense biliary obstruction. A few hours later, when the animal appeared to be dying, the bilirubin in the serum had increased, but gave a biphasic delayed reaction. In the fifth animal a slight increase of bilirubin was evident three days after the common bile duct had been tied, and a biphasic delayed reaction resulted. On the fourth day the increase was more marked, and the van den Bergh reaction was now of the prompt direct type.

These experiments, which require careful repetition, show the fallacies and difficulties of dealing with animal experiments only. The variations found in the van den Bergh reaction at different stages of obstruction must, however, until more facts are known, add caution to the interpretation of results in human cases of obstructive jaundice.

The occurrence of 'biliary thrombi' in the bile capillaries, and their relations to obstructive jaundice, require mention. These thrombi, first described by Eppinger, are more characteristic of other forms of jaundice, but are well seen in many cases with obstruction. Certainly they are by no means confined to cases with pleocholia, or excessive bile secretion, and the most sensible suggestion of their origin seems to be, in the writer's opinion, that they depend on damage to the liver-cells so that an abnormal bile is excreted. It may be, as some have suggested, that the bile contains albuminoid substances, which would bring these

thrombi closely into comparison with the tube-casts in nephritis. The evidence is all against biliary thrombi being of importance in the development of obstructive jaundice.

The gross causes of obstruction in the bile passages bring up some points of great interest. The direct mechanical effects of impacted gall-stones or tumours are sufficiently obvious. But does a pure cholangitis, or inflammation of the bile ducts, ever lead to *complete* obstruction? Naunyn (1919) has written on this question at great length, and firmly believes that total obstruction arises in this way. On the other hand, French writers, such as Brulé, believe that ascending or descending inflammations of the bile ducts lead to functional derangement of the liver-cells far more than to mechanical obstruction. The question must remain open for the present, but in passing it may be pointed out that the essential pathology of so-called 'catarrhal jaundice' is intimately concerned with its solution.

It seems probable, as is seen in the section following, that damage to the hepatic cells and partial obstruction from cholangitis are frequently combined.

Toxic and Infective Hepatic Jaundice.

This group includes a great number of cases of jaundice within its boundaries, and is, in fact, the commonest variety met with clinically. It includes the jaundice which occurs:

- (a) as a complication of many acute fevers—pneumonia, typhoid, spirochaetal jaundice;
- (b) after the administration of certain drugs—chloroform, salvarsan, phosphorus;
- (c) after damage to the liver-cells of an unknown kind—acute and subacute yellow atrophy of the liver;
- (d) after many general conditions of infection and toxæmia—acute sepsis, cardiac valvular disease with 'back pressure'.

There is, again, a great diversity of opinion as to the mechanism of this variety of icterus. The chief view in Germany is really due to Naunyn (1919), who holds that cholangitis, or inflammatory changes in the finer or larger bile passages, is the basis of this type of icterus. If this were correct, then this large group could obviously be included under the heading of obstructive hepatic jaundice.

While, however, a lesion in the bile passages has been especially emphasized in Germany, changes in the liver-cells themselves, ranging from simple functional derangement (unrecognizable microscopically) up to actual necrosis, have in France and other countries been considered as the main aetiological factor.

The present writer has dealt in a recent article (1922) with the question of damage of liver-cells and its relation to jaundice. He considers that the varying degrees of hepatic insufficiency, many of them accompanied by jaundice, may be associated with histological changes ranging from simple cloudy swelling (as in pneumonia), through fatty degeneration (as in chloroform poisoning), partial

necrosis and dislocation of liver-cells (as in spirochaetal jaundice), up to almost complete and total necrosis of the liver (acute yellow atrophy). The combination of syphilis with salvarsan treatment may be taken as an example of circumstances under which any one of the different degrees of hepatic damage associated with jaundice may be met with.

In close confirmatory relation to the question of damage to liver-cells as an aetiological factor in jaundice, there is the evidence now available of disturbance in other hepatic functions, recognizable by such means as the laevulose tolerance test. This test is now known to give evidence of acute hepatic damage, whether associated with icterus or in the absence of that sign. It is positive in most cases of early jaundice, excepting those of haemolytic origin.

It seems probable that, in this large group of jaundice, both damage to the hepatic cells and obstruction in the bile passages from cholangitis play a rôle preponderating one way or the other at different times. Such a view fits in well with the theory of jaundice which has been proposed, and with the results of the van den Bergh reaction. It is in this group of cases of jaundice that the occurrence of biphasic reactions was first noted by Feigl and Querner (1919). This type of reaction, as has been already stated, is best explained by assuming that some bile pigment fails to pass through damaged liver-cells and passes on directly into the blood, while the remainder, which is excreted by still active liver-cells, is obstructed in the bile capillaries and reabsorbed into the circulation.

Haemolytic Jaundice.

This variety of icterus requires nowadays to be brought into line with three series of observations:

1. The invariable occurrence of a delayed direct van den Bergh reaction, or of so delayed a reaction as to be taken as negative.
2. The frequent absence of bile pigment from the urine, and its constant presence in the faeces (acholuric jaundice).
3. It must be considered in relation to all the newer work on the reticulo-endothelial system, and on the functional relationships of spleen and liver (Eppinger's *Die hepato-lienalen Erkrankungen*).

The possibility of occurrence of a true icterus by haemolysis, with which the liver is not essentially concerned, has given rise to endless discussion. Beginning with Virchow's (1847) observations on haematoidin, an isomer of bilirubin, the older writers believed in the occurrence of a true haemolytic icterus, without obstruction and without the action of the liver-cells. This view lost ground completely after the publication of the experiments of Minkowski and Naunyn in 1886. These experiments were carried out on geese, the liver being extirpated by operation. Thereafter the animals were at once poisoned with arseniuretted hydrogen, a gas which in normal birds produces an intense haemolysis, and either a rapidly developing icterus or haemoglobinuria. The former occurs where haemolysis is of moderate degree, the latter where blood destruction is

rapid and intense. The experiments seemed to show that in the absence of the liver no jaundice resulted. It is in a way remarkable how the few observations carried out in this way were accepted on all sides without subsequent control, since they swept aside for many years the idea of a true haemolytic jaundice.

Stadelmann (1891) brought forward the next important observations, using as blood-destroying agents in animals both arseniuretted hydrogen and toluylendiamine. To him is due the theory of jaundice arising by 'pleocholia', the excess of pigment in the bile being thought to render it thick and viscid, and so bring about stasis and obstruction in the finest bile capillaries.

About this time, too, there appears the earliest suggestion of functional disturbance of the liver-cells, Pick (1892, 1894) and others developing the view that this form of jaundice, in which no evidence of actual obstruction could be found macroscopically, might arise by the liver-cells excreting bile pigment backwards into the vascular capillaries instead of into the bile canaliculi.

Eppinger's work (1902, 1908) next assumed prominence, following his description of 'biliary thrombi'. These he found to occur most characteristically in haemolytic jaundice, although not confined to that group. In his view the icterus was to be explained by obstruction of the finer bile ducts brought about by biliary thrombi.

It will be noticed that the whole of the above experimental work was carried out in Germany, Virchow having set on foot an era of great advances in pathology, which gave for the time being, as far as the subject of jaundice is concerned a preponderating rôle to the literature of that country.

The year 1911 seems to mark the beginning of a new chapter in the study of haemolytic jaundice, which has attempted to establish two main propositions:

1. That bile pigment can be formed from haemoglobin outside the liver altogether, and without the intervention of the glandular cells of the liver at all.
2. That in the pathogenesis of the various clinical forms of haemolytic jaundice the spleen and its functional activities are of the greatest importance. This proposition has, of course, received clinical proof by the cure of cases of haemolytic jaundice by splenectomy.

The scientific work which has led up to the views put forward may now be discussed. Three main groups of observations, carried out in America, in France, and in Germany, require special mention in this connexion. It is wellnigh impossible to attempt to cover the ground in anything like chronological order.

Beginning in 1911, a long series of articles appeared in the *Journal of Experimental Medicine* on 'The Relation of the Spleen to Blood Destruction and Regeneration, and to Haemolytic Jaundice'. This work was done by Richard M. Pearce, then of Philadelphia, and many co-workers—Austin, Karsner, Peet, Eisenbrey, Musser, Krumbhaar, &c. A summary of these papers would be beyond the scope of a brief review, but in them are contained many observations on animals, before and after splenectomy, which are of great importance in relation to cases of jaundice associated with splenomegaly.

About the same time important experimental work also began to be pub-

lished by Whipple and Hooper, working in Baltimore. Their first experiments (1911) dealt with the results of the intravenous injection of haemoglobin into normal dogs, and also into dogs with an Eck fistula, by means of which the blood-supply of the liver is cut down to about one quarter of the normal. They found that depletion of the hepatic blood-supply in this way neither prevented nor delayed the occurrence of icterus, although its intensity was diminished. They concluded from these experiments that the liver could not be the essential factor in the rapid change of haemoglobin into bile pigment which occurs in the circulation within a very few hours. Their next series of observations (1913) was an attempt to clinch their previous conclusions in a way free from all error. Their crucial experiments consisted in the intravenous injection of haemoglobin into:

(a) dogs in which the liver, spleen, and intestines had been shut out of the circulation;

(b) dogs with a 'head and thorax' circulation only.

It was found in both sets of experiments, even in those where a 'head and thorax' circulation was alone kept up, that the haemoglobin was rapidly changed, in part at least, into bile pigment within the circulating blood. These experiments have been widely accepted as proving conclusively that in dogs, at least, haemoglobin can be readily changed into bile pigment within the circulation, under conditions in which the whole of the abdominal viscera, including the liver and spleen, have been completely shut out. These results do not appear to have been controlled by others, partly, no doubt, because of the difficulty in the operative technique required. In view, however, of their fundamental importance, the writer, with Dr. B. Prusik, of Prague, has undertaken their repetition, using, of course, a far more delicate method of detecting bilirubin in the serum (the van den Bergh test) than was available to Whipple and Hooper. The experiments are not yet complete, but in eight dogs in which the identical technique of Whipple and Hooper for obtaining a 'head and thorax' circulation was employed, bilirubin could not be demonstrated in the serum after the intravenous injection of haemoglobin, even with the delicate test employed.

The very important experiments of Whipple and Hooper thus remain, for the present, unconfirmed.

In 1912 the present writer, while working in Aschoff's laboratory on haemolytic anaemias and haemolytic jaundice, repeated the well-known experiments of Minkowski and Naunyn (1886) which have already been referred to. Geese were again used for the experiments, the liver was extirpated by operation, and arseniuretted hydrogen used to produce haemolysis. It was found that icterus was absent or slight under such experimental conditions, which was so far confirmatory of the previous work. But it was recognized that in birds such as geese removal of the liver brings about a set of circumstances entirely different from removal of that organ in higher animals. In the goose the liver is extremely large, and (as in all birds) the spleen is small and poorly developed. Moreover, it was noticed that in the bird's liver there is a quite extraordinary

number of endothelial cells (Kupffer cells) lying along the walls of the vascular capillaries. These cells normally give a diffuse iron reaction, and are evidently concerned with part at least of the metabolism of haemoglobin. The writer showed by experiment that in normal geese, with an intact liver, poisoning with arseniuretted hydrogen led to great functional activity and proliferation of these cells, which finally might even become detached and circulate freely in the bloodstream. In these cells debris of red corpuscles, haemosiderin (giving the Prussian blue reaction), and bright green biliverdin could frequently be recognized together. Without going into full details, the writer came to the conclusion that icterus was absent in the geese from which the liver had been extirpated, because in removing the liver all the Kupffer cells had at the same time been taken away. In man, and in the higher animals, these cells are far less abundant in the liver, but the spleen is developed as a much larger organ, containing in its meshes abundant endothelial cells which are known, even in human pathology, to be intimately concerned with destruction of red blood corpuscles. It is thus suggested by this work that in removing the liver of birds there is obliterated at the same time the tissue which corresponds closely to the spleen in higher animals.

It is impossible to pursue this line of experiment in higher animals, since death occurs within a very short time of any operative removal of the liver. Hence the absolute necessity for experiments of the kind undertaken by Whipple and Hooper.

Interesting results have, however, followed the subsequent development and amplification of the writer's experiments on birds by Lepehne (1917). This work was carried out first of all on pigeons, which, like geese, have a small spleen and large liver, and the proliferation and activities of the abundant Kupffer cells of the liver were fully confirmed in experimental icterus induced by arseniuretted hydrogen. Lepehne then transferred his experiments to rats, in which the spleen is large and highly developed. Following splenectomy he was able to observe the scanty Kupffer cells of the liver increase greatly in number, and soon they showed phagocytosis of red corpuscles and a diffuse iron reaction. Further, he found that if the proliferated Kupffer cells were put out of action by loading them with collargol introduced intravenously, the onset of experimental icterus was either prevented or greatly delayed when compared with control animals in which the collargol injections were omitted. Thus Lepehne came to agree fully with the view that what corresponds to the spleen in higher animals is largely enclosed within the liver of birds.

The Kupffer cells of the liver and the endothelial cells of the spleen form an important part of Aschoff's reticulo-endothelial system. The result of this experimental work is thus to suggest that the cells of this system, whether in the liver or spleen or both, are actively concerned in the mechanism of haemolytic jaundice, and not the polygonal glandular cells of the liver at all.

French investigators had meanwhile been approaching the subject by an entirely different route. Widal, Arami, and Brulé (1911) had given reasons why it was impossible to account for haemolytic icterus on the basis of an obstruction

within the liver. They showed that haemolytic jaundice was a form of 'dissociated jaundice', and that while bile pigment accumulated in the tissues, bile acids passed out normally into the intestine. Further, Chauffard, Laroche, and Grigaut (1911) were able to demonstrate that the third important constituent of the bile, namely, cholesterol, does not accumulate in the blood-serum as in all cases of obstructive jaundice. This French work, therefore, seemed to show that the condition in haemolytic jaundice was one of 'pure pigmentary cholaemia'.

French workers have also laid great stress on the change of haemoglobin into bile pigment, outside the liver, within different cavities of the body. This has been fully confirmed by a great number of observers, but it must be admitted that, under such circumstances, icterus does not actually appear. It may be, of course, that the bilirubin is not absorbed through the pleural or peritoneal cells as such, but is changed into urobilin.

Various writers have also claimed that the blood coming from the splenic vein contains more bilirubin than the blood of the splenic artery. This opinion is strongly supported by Hijmans van den Bergh (1918), who claims that in dogs poisoned by phenylhydrazin an increase of bilirubin (up to three times) can be demonstrated in the splenic vein with great certainty.

The view now put forward with regard to the origin and mechanism of haemolytic icterus is, therefore, as follows, it being understood that actual proof of the theory is still wanting in various respects.

It is suggested that haemolytic jaundice depends on blood destruction in excess of the normal, whereby the cells of the reticulo-endothelial system, especially of the spleen in man and the higher animals, are thrown into over-activity. This over-activity may result in, or be actually dependent on, increase in size of the spleen or splenomegaly. The exact position of the somewhat scanty Kupffer cells of the liver in this mechanism, in man and the higher animals, is not known, but it seems probable that their rôle is less important than the spleen in virtue of bulk alone.

It is suggested that following excessive blood destruction an exaggerated amount of bile pigment is formed by the reticulo-endothelial cells, circulates in the blood, and gives rise to icterus. This bile pigment is formed quite independently of the glandular cells of the liver, and probably does not pass through them at any time.

The bilirubin found in the blood in haemolytic jaundice gives a delayed direct reaction, or frequently none at all, with the van den Bergh test. The same reaction is given by the small amount of bilirubin found in the blood-serum of all normal individuals. The view is therefore put forward that in haemolytic jaundice the blood-serum contains a greatly increased amount of bilirubin of the same type as that arising from the normal physiological destruction of effete red blood corpuscles in health.

The whole group of cases of haemolytic jaundice, along with other closely allied diseases such as splenic anaemia, pernicious anaemia, and Banti's syndrome, have been included by Eppinger and Ranzi (1920), on the views suggested above,

in an important recent monograph under the title *Die hepato-lienalen Erkrankungen*, or 'Liver-spleen Diseases'. In all of these diseases the serum contains an excess of bilirubin, which gives the delayed direct reaction only with the van den Bergh test. In some of them icterus is definite, in others it is of latent type. In all the stools are of normal colour, and the urine is generally free from bile pigment. The writer prefers, in the present review, to omit all controversial discussion of the origin and significance of urobilin in the urine in this and other groups of jaundice.

Clinical Observations on Jaundice with the Hijmans van den Bergh Reaction.

In view of the important theoretical and practical results which have followed the application of this method in the study of jaundice, it seems right to include a section under the above heading. Many hundreds of cases have now been investigated, both where obvious jaundice exists and where the possibility of its development is suspected. The chief published papers to which the writer has had access are those of Hijmans van den Bergh (1918), Lepehne (1919, 1920, 1921), Rosenthal and Holzer (1921), and Feigl and Querner (1919), but many other investigations on special outbreaks and special types of jaundice are now in print.

The chief points of interest may be summarized quite briefly under the following headings:

The bilirubin content of normal serum. Hijmans van den Bergh has by his method completely established the fact, affirmed by Gilbert and others since 1906, that normal human blood-serum always contains a small amount of bilirubin, which is only detected by the indirect reaction. In his monograph the values found are given as between 1 in 400,000 and 1 in 250,000, the comparison being made with a solution of chemically pure bilirubin. In a later paper, published in France, van den Bergh gives figures for the bilirubin content of normal human serum of from 1 in 1,000,000 to 1 in 400,000, and, taking as his 'unit' of bilirubin the figure 1 in 200,000, it would therefore appear that 0.2 to 0.5 of a 'unit' is the normal physiological limit. Lepehne found the average figure in a series of patients, not suffering from jaundice, to be $\frac{0.3}{200,000}$, or 0.3 of a unit, and similar results have been obtained by the writer and others. The bilirubin found in normal serum is now frequently referred to in the literature as 'functional bilirubin'.

Van den Bergh also made the important observation that in some apparently healthy individuals of sallow complexion the bilirubin content of the serum may show figures ranging up to 1 in 80,000, or nearly three units. Such individuals had previously been recognized by Gilbert and Lereboullet (1905) in France, who gave to this condition the name of 'simple familial cholaemia'. In cases of this kind the spleen is as a rule not enlarged, the urine contains neither bile nor urobilin, and the resistance of the red blood corpuscles to haemolysis by weak

millionths
1-2.5
normal blood

Aw 1.5

cholaemia
12.0

saline solutions is not diminished. Van den Bergh, however, noted the important point that in a few instances the spleen is slightly enlarged and urobilin present in the urine. He has made the suggestion that these latter cases are on the border line between 'physiological hyperbilirubinaemia' and the actual disease known as haemolytic (acholuric) jaundice.

The bilirubin content of the gall-bladder. Bile from the gall-bladder always gives a prompt direct reaction to the test. The value in units of bilirubin varies enormously, as is to be expected, even under more or less normal conditions. In bile draining from a biliary fistula several days after an operation for gall-stones, van den Bergh found a bilirubin content of 1 in 3,000 to 1 in 4,000.

The bilirubin content of haemorrhagic exudates into serous cavities (extra-hepatic bile formation). Bilirubin obtained from such exudates gives the delayed direct reaction only, or frequently a negative result. The presence of bilirubin is therefore determined by application of the indirect test. Van den Bergh gives records of three cases of this kind in which quantitative estimations of bilirubin were made:

- | | | |
|--|------------------------|-----|
| 1. Traumatic haematoma of the knee-joint
(65 c.cm. fluid) | Bilirubin 1 in 23,000. | 40 |
| 2. Sarcoma of the lung with large haemorrhagic pleural exudate | Bilirubin 1 in 30,000. | 30 |
| 3. Traumatic subdural haematoma (150 c.cm. fluid) | Bilirubin 1 in 4,000. | 250 |

It is thus evident that large amounts of bilirubin may be formed extra-hepatically in haemorrhagic effusions. It is further of interest to point out that in the second case (sarcoma of lung) the bilirubin content of the blood from the general circulation was examined at the same time and found to be 1 in 360,000.

Obstructive hepatic jaundice. Here all who have made use of the test are in full agreement as to the results. In jaundice due to complete obstruction a prompt direct reaction is always obtained, the violet-blue colour attaining its maximum within 30 seconds. In such cases the amount of bilirubin present in the serum may be enormous, and van den Bergh gives figures up to 1 in 4,000 (50 units). It will be seen that this figure actually equals that quoted for bile from a gall-bladder fistula!

It is important to point out, a fact now well recognized by all workers, that in obstructive jaundice the colour of the skin gives no indication whatever of the extent of the bilirubin content of the serum. In a case of chronic 'green' or 'black' jaundice the bilirubin content of the serum may be far lower than at the early stage of obstruction, when the patient is just beginning to show a yellow tinge.

Important facts have also emerged regarding the threshold value of the kidney for bilirubin in obstructive hepatic jaundice. All who have investigated the matter, including van den Bergh, Lepehne, and the writer, are agreed that bile pigment appears in the urine whenever the content of the serum reaches

Bile
250-300

40

30

250

3

obs jaundice
up to 250

about 4 units (1 in 50,000). Below this figure, biliuria is absent, and a condition of 'latent' obstructive jaundice may exist.

Haemolytic jaundice. In true haemolytic jaundice the van den Bergh reaction is always of the delayed direct type, or so delayed as to be taken as negative. The bilirubin content of the serum in such cases never reaches the same height as in obstructive jaundice, but Rosenthal and Holzer (1921) give figures in such cases ranging from 4.5 up to 18.5 units. The highest figure obtained by the writer in a case of this kind was 11 units.

The threshold value of the kidney for the bilirubin in haemolytic jaundice is entirely different from that obtaining in the obstructive variety, and in fact it may be doubted if in true haemolytic jaundice, without some added complication, bilirubin ever passes through the kidney at all. In the writer's own case, in which 11 units of bilirubin were present in the serum, not a trace of biliuria was ever observed. The suggestion has been strongly made that in these cases the bilirubin only escapes in the urine as urobilin, and certainly urobilinuria is a well-known phenomenon in cases of haemolytic jaundice.

The recognition of latent forms of haemolytic jaundice is an important development due to the van den Bergh reaction. This is referred to under a separate heading.

Latent jaundice. The recognition of this condition is a direct development of the van den Bergh method, since none of the methods previously employed were suitable for estimating small increases of bilirubin in the blood-serum. By latent jaundice is now understood a retention of bile pigment (and frequently of bile acids as well) in the blood-serum, insufficient in amount to colour the skin and mucous membranes, and not giving rise to biliuria. The absence of bile in the urine presupposes, in the case of latent obstructive jaundice, an amount of bilirubin in the blood of less than 4 units. In the case of latent haemolytic jaundice, this does not hold, as has been already stated.

The most important disease now brought into the category of latent jaundice is pernicious anaemia. In this haemolytic disease a lemon yellow coloration of the skin is almost the rule, but that this indicated a minimal degree of icterus was scarcely suspected. Syllaba (1912) and Scheel (1912) had, however, previously described an increased bilirubin content of the serum in this disease, before the introduction of the van den Bergh test. Van den Bergh showed that the bilirubin content of the serum is increased in every case of pernicious anaemia, the increase amounting to 5 or 6 units in severe cases. The average figure is, however, between 3 and 4 units in most of the published results. The bilirubin in this disease gives, of course, the delayed direct reaction, or generally no reaction with the direct test at all. The same type of latent haemolytic jaundice has been observed in bothriocephalus and other worm anaemias (Lepehne), and is a constant feature in the serum of all new-born children (see Icterus neonatorum).

Latent icterus of the obstructive type occurs commonly enough in many chronic hepatic diseases, such as cirrhosis, and in a certain percentage of meta-

raising threshold

20

20-90

not this
delayed direct
threshold for
this type

Pernicious
anaemia

15-20 (-30)

static tumour growths. In such cases a prompt direct reaction is obtained with the test, but owing to the small amount of bilirubin (commonly 2 or 3 units) difficulty may be met with in detecting the immediate colour-change unless the serum to which the diazo reagent is added is closely compared with a control specimen.

The occurrence of latent icterus has recently been applied to a very practical problem. Jaundice, even fatal in severity, is a well-known complication in the salvarsan treatment of syphilis, and at the request of the writer Lieut-Commander Gerrard, R.N., has recently investigated the bilirubin content of the serum in patients undergoing a course of this treatment. His results are as yet unpublished, but it may be stated meantime that by the recognition of the onset of latent icterus he has been able on various occasions to prophesy the development of obvious jaundice on continuation of the arsenical treatment.

Although not concerned with the clinical application of the van den Bergh reaction, it would be unfortunate to omit here a brief reference to the French outlook on latent jaundice. French workers have paid special attention to changes in the urine and faeces, leaving consideration of changes in the blood-serum severely alone. In this way, however, and by a different route, the occurrence of latent jaundice has been fully recognized. The first work quoted by Brulé is that of Brault and Garban (1914), who were investigating cases of alcoholic cirrhosis of the liver. In these patients, none of whom were jaundiced, bile salts were found in the urine. Bile pigment was absent, but on the other hand urobilinuria was constantly present. On these results a condition of latent icterus was inferred to exist, and confirmatory work has been published by other French writers.

It would appear to be well established, both from work with the van den Bergh reaction, and by the methods employed by French writers, that latent jaundice is of fairly common occurrence in disease. The recognition of retention of bile acids, in the absence of overt jaundice, may yet prove to be a fact of some clinical importance to physicians and dermatologists.

Toxic and Infective Hepatic Jaundice.

In this, the largest of all the groups of jaundice, the application of the van den Bergh reaction has given little clinical help, because of the variability in the results. It was in cases of this kind that biphasic reactions were first observed by Feigl and Querner (1919). The theoretical explanation of biphasic reactions has already been discussed, and it would appear that the amount of each of the two kinds of bilirubin in the serum must depend on whether damage to the liver cells, or obstruction from cholangitis, is the principal factor at work. This view is strengthened by facts observed in repeated examinations of the same case of jaundice, and instances have been observed of the serum gradually passing through the whole range of the results obtainable with the van den Bergh test.

This change of reaction to the test is well demonstrated in the clinical study

of so-called *catarrhal jaundice*. In the first cases of this kind investigated by the writer the van den Bergh reaction was of the delayed direct type, and the inference was drawn that a pure functional derangement of the liver-cells was the characteristic lesion in this type of jaundice. Subsequent investigations have shown, however, that this inference was erroneous, since in recent cases of this kind the van den Bergh reaction has been either of the prompt or biphasic type. Schiff and Eliasberg (1922) have examined an interesting group of over 30 cases of catarrhal jaundice, occurring in children during the winter 1921-22. All the cases appeared to be more or less identical clinically, but the sera behaved differently to the van den Bergh test. Between October 1921 and the beginning of January 1922, all the sera examined gave the delayed direct reaction only. To their astonishment, however, a prompt direct reaction was obtained in all subsequent cases, without the least apparent change in the clinical picture. In none of the cases were the stools free from bile, although clay-coloured. The duodenal contents were examined in 26 patients, and in all of them both bile pigment and bile acids are said to have been present in the intestine. There seems little doubt from the above work that catarrhal jaundice is to be regarded as a combination of toxic and infective with obstructive jaundice.

Icterus neonatorum. The van den Bergh test has given very interesting results in connexion with the aetiology of this variety of jaundice. Van den Bergh had noted that in the blood of all children at birth—the sample being taken from the umbilical vein—there is a ‘physiological bilirubinaemia’. This matter was followed up at his instigation by Hirsch, who found that the bilirubin content of the serum at birth varied between 1 in 30,000 to 1 in 100,000. Taking the higher figure (1 in 30,000), this would mean, in the absence of obvious jaundice, an amount of bilirubin of at least eight times the normal figure for an adult. Hirsch claimed that the height of the bilirubin content at birth ran parallel with the subsequent occurrence of icterus neonatorum, but van den Bergh himself was unable to confirm this view. Lepehne (1921) examined small samples of blood, obtained from the sole of the foot, in seven children seen within a few days of birth, who showed definite icterus. A quantitative test was not possible with the small samples available, but the qualitative test was in every case negative or greatly delayed with the direct test. The writer has examined the blood-serum of ten newly-born children, the sample being obtained from the umbilical vein. In all of them the bilirubin was increased, the highest figures obtained being just over 3 units (1 in 60,000). In all cases the direct reaction was negative, or so greatly delayed that its occurrence was not waited for. In two children in which figures of 3 units were found, icterus is said to have been definitely visible a few days later. The infants were, however, from the midwifery practice outside the hospital, and no serum could be obtained from them after icterus had appeared.

The above results make it clear that icterus neonatorum behaves, in respect of the van den Bergh test, similar to the group of haemolytic jaundice, and quite different from icterus due to obstruction.

serum at birth
10-30

It would be tedious to deal further with clinical observations carried out with the methods of van den Bergh, but one point of great interest to the clinician may simply be mentioned in conclusion. It was obviously important to see whether the presence of gall-stones, without obvious attacks of colic and without visible jaundice, was associated with any alteration in the bilirubin content of the serum. Sufficient results are now available to show that in patients who have gall-stones, without icterus, the bilirubin content of the serum is normal.

Dissociated Jaundice.

Although in the present state of our knowledge of jaundice it is impossible to deal adequately with the changes which occur in all the constituents of the biliary secretion, reference must be made to the discovery by French observers of what is described by them as 'dissociated' jaundice. The dissociation affects two of the chief constituents of the bile, namely, the bilirubin and the bile salts, and in certain cases of hepatic disorder it has been claimed that one of these substances may be retained or reabsorbed into the blood while the other is excreted in the normal way.

Almost all the work on this subject is French, and is fully reviewed in Brulé's (1922) monograph, while an article by Lemierre, Brulé, and Garban (1914) gives the bibliography of the subject. An American article by Hoover and Blankenhorn (1916), containing some criticisms of the French observations, is the only other published account to which the writer has had access.

Brulé (1922) draws attention to certain observations of older writers, which he thinks have never been thoroughly appreciated. Graves had noted the occurrence of pruritus several days, or even weeks, before icterus developed. Murchison has seen bradycardia in hepatic diseases without jaundice. Salkowski had found bile salts absent from the urine in several cases of obstructive jaundice.

The first important observation was made by Widal, Abrami, and Brulé (1907) while engaged in a study of haemolytic icterus. They showed that this depended solely on an increase of bile pigment in the blood, the bile salts continuing to pass out into the intestine. This observation was used at the time as an additional proof of the occurrence of a true haemolytic icterus. This observation led on Lemierre and Brulé (1910) to the discovery that dissociation could also occur in certain forms of icterus where there was no doubt that the hepatic cells were involved. Since then fairly numerous contributions, both clinical and experimental, have been made to French literature. It would appear that pigmentary retention, with normal excretion of bile salts, is particularly common in the later stages of catarrhal jaundice, while the stools are still clay-coloured. This form of dissociation, with retention of bile pigment alone, is, according to the French view, the commoner variety met with. Retention of bile salts, with normal excretion of pigment, has been seen in certain cases of cirrhosis of the liver, and may be associated with itching and

bradycardia. If the occurrence of urobilin in the urine were not regarded by Brulé and others as definite evidence of slight retention of bile pigment, then this second form of dissociation would be almost the rule in cases of cirrhosis.

Brulé quotes experimental work on animals by himself and Lemierre with sera having a cytotoxic action on the liver, and by Noël Fiessinger and Lyon-Caen (1910) with phosphorus, in support of the clinical observations described above.

Are we to accept on the above evidence the occurrence of dissociated jaundice as a firmly established fact?

Haemolytic jaundice may certainly be accepted as a dissociated condition, since it is now well established that in it there is an increase of bilirubin alone in the blood, along with a normal hepatic function, both bile pigment and bile acids passing out into the intestine in the usual way. It is doubtful, however, if the term dissociation in the sense which has been given to it is applicable here.

When we come to the question of dissociation in connexion with truly hepatic icterus, then the arguments used by the French school appear much less certain in their application. Hoover and Blankenhorn (1916) have seized on certain weak points, but so far confirm the French work by stating that in two cases of primary anaemia, and in two cases of lead-poisoning, bile salts were present in the blood in large amount without any excess of bile pigment. These writers lay stress on an obvious source of fallacy in all the French work, namely, that all the attention has been directed to the presence or absence of bile salts and bile pigment in the urine or faeces, the conditions in the blood plasma not being taken into account. Hoover and Blankenhorn carried out their work by estimating the bile pigment and bile salts in the blood itself, and lay stress on what they term the adsorptive power of the serum for the biliary constituents. They recognized that the serum might contain a great excess of bile pigment which is never filtered out by the kidney, and they state that the tissues may show under such circumstances no trace of yellow coloration. Except in cases recognized as haemolytic jaundice, they found no instance in which the pigment was retained while the bile salts passed out normally into the intestine. They did find occasionally what they describe as 'renal dissociation', namely, the retention in obstructive jaundice of both pigment and bile salts in the blood, but the filtration of bile salts only through the kidneys. The urine thus contained bile salts, but pigment was absent.

So far no complete examination of the question of dissociated jaundice appears to have been made with the help, as regards the pigmentary changes, of the van den Bergh reaction. Until this is done, it may be safer to reserve judgement on the importance and frequency of occurrence of a true dissociated jaundice.

APPENDIX.

Technique of the Hijmans van den Bergh Reaction.

One of the great merits of the test is the small amount of blood-serum required, and for the qualitative test as little as 0.5 c.cm. of serum can suffice. The result is certainly easier to read, however, when 1 c.cm. is available. For the quantitative colorimetric test 1 c.c. of serum is sufficient. The blood is obtained from a vein by acupuncture, allowed to clot in a dry test-tube, and the separated serum is then removed by a pipette.

Apparatus and reagents required. A. For the qualitative test.

1. A few small test-tubes, which must be perfectly clean.
2. Freshly prepared Ehrlich's diazo reagent. This consists of two solutions, each of which keeps well, but the mixture must only be made immediately prior to the test. The two solutions are made up as follows, and it will be noted that van den Bergh uses a small quantity of sulphanilic acid, which differs from the more usual prescription.

<i>Solution A.</i>	Sulphanilic acid	1 gm.
	Concentrated HCl	15 c.cm.
	Distilled water	1,000 c.cm.
<i>Solution B.</i>	Sodium nitrite	0.5 gm.
	Distilled water	100 c.cm.

The diazo reagent consists of a mixture of these two solutions in the proportion of 25 c.cm. of *A* to 0.75 c.cm. of solution *B*.

3. A graduated 1 c.cm. pipette.
4. Absolute alcohol (96 per cent.).
5. A centrifuge and centrifuge tubes.

The qualitative test is then carried out as follows :

A. The direct reaction. To 1 c.cm. of the serum, which van den Bergh dilutes with 2 c.cm. or more of distilled water, 0.25 or 0.5 c.cm. of freshly prepared diazo reagent is added. One of three events may now occur.

1. *A prompt or immediate direct reaction.* A colour change begins immediately, and is maximal in 10 to 30 seconds. The colour is a bluish-violet, of intensity depending on the amount of bilirubin present. This type of reaction is particularly characteristic of jaundice due to complete obstruction.

2. *A delayed direct reaction.* This begins only after 1 to 15 minutes, or even very much longer, and consists in the development of a reddish coloration, which gradually deepens and becomes more violet. This type of reaction, which is particularly characteristic of haemolytic jaundice, is not made use of further, the presence of bilirubin being determined with certainty by going on at once to the application of the indirect reaction.

3. *A biphasic direct reaction.* In this a reddish colour appears at once, which either slowly or quite rapidly deepens to violet. According as the

reaction approaches more closely to the prompt or delayed types, a division is now made into biphasic prompt and biphasic delayed reactions.

B. *The indirect reaction.* This is applied to identify bilirubin where the direct reaction is of the delayed type, or, as often happens, completely negative for practical purposes because of its slow development. The indirect reaction is also required for the quantitative estimation of bilirubin. It is carried out as follows: To 0.5 c.cm. of serum add 1 c.cm. of 96 per cent. alcohol. The mixture is made in a centrifuge tube, which is then centrifugalized until all the albuminous precipitate has sunk to the bottom to leave a clear yellowish supernatant fluid. Little pigment is lost in sera giving a delayed reaction only, by absorption into the precipitate. Greater loss occurs in sera giving the prompt direct reaction, and this is a recognized fallacy in the quantitative test. It happens frequently that the supernatant fluid is not clear, but opaque from the presence of fatty substances. The opacity can be removed by adding a drop or two of ether, or 0.5 c.c. or more of alcohol.

To 1 c.cm. of the yellow supernatant fluid is now added 0.25 c.cm. of diazo reagent. A violet-red colour appears in the presence of bilirubin, and is maximal almost at once.

The quantitative test. This consists of a colorimetric application of the indirect reaction described above. The comparison was at first made by van den Bergh with a standard alcoholic solution of pure bilirubin to which the diazo reagent was added, but later an artificial standard solution was made in view of the practical difficulties in obtaining pure bilirubin. For this method some simple form of colorimeter is very convenient, and the writer has found the Autenrieth-Funk pattern very suitable, but any variety may serve. Fairly accurate results can be obtained by simple methods of dilution in small test-tubes of equal calibre. Such results are ample for all clinical purposes, since no colorimetric method of this kind can ever pretend to more than tolerable accuracy.

The artificial standard solution (van den Bergh). This consists of iron sulphocyanide dissolved in ether. The solution is made up of a colour corresponding with a solution of azobilirubin of 1 in 200,000. The standard solution is made up as follows: Dissolve 0.1508 grm. of ammonium iron-alum in 50 c.cm. concentrated HCl, and add water to 100 c.cm. This gives a solution of 1 in 320 normal, which keeps indefinitely.

To 10 c.cm. of this solution add 25 c.cm. concentrated HCl and water up to 250 c.cm. This gives a dilution of 1 in 8,000 normal, which keeps for about six months.

To 3 c.cm. of this solution add an equal volume of 20 per cent. potassium sulphocyanide and 12 c.cm. of ether. Shake well, and when all the reddish colour has passed into the ether, transfer the ether carefully into the colorimeter or other comparative tube. This solution is in a concentration of 1 in 32,000 normal, and must be prepared freshly each day a test is made. It corresponds in colour, as has been indicated, to a 1 in 200,000 solution of azobilirubin, or 1 unit of bilirubin.

In the carrying out of the colorimetric test with the indirect reaction the chief point of importance is, of course, to take note of *the amount of dilution of the serum* necessary in the various steps of the test. Van den Bergh gives the following figures in respect of this dilution. He states that if 0.5 c.cm. of serum is precipitated with 1 c.cm. of alcohol, and centrifugalized, a volume of $\frac{10}{7}$ c.cm. is left above the precipitate. The amount of pigment lost in the precipitate is neglected, and it is taken that the bilirubin in 0.5 c.cm. serum is now contained in $\frac{10}{7}$ c.cm. supernatant fluid, or is diluted $\frac{20}{7}$ times. To 1 c.cm. of this supernatant fluid is added 0.5 c.cm. of alcohol, and 0.25 c.cm. of diazo reagent. The volume of fluid is thus increased from 1 c.cm. to 1.75 c.cm., being a dilution of $\frac{7}{4}$. The addition of 0.5 c.c. of alcohol gets rid of any opacity, and also helps to bring the ultimate dilution to a round figure.

Thus, the dilution of the original serum, in this fluid which is used for the colorimetric test, is $\frac{20}{7} \times \frac{7}{4} = 5$ times.

Thus, if on carrying out the test the test fluid is found to be identical in intensity of colour with the standard solution (which equals 'one unit' of bilirubin), then if the dilution had been made according to the method described, the serum would actually contain not 1, but 5 units of bilirubin, having been diluted that number of times. Normal human blood-serum contains 0.2 to 0.5 of a 'unit' of bilirubin (i.e. 1 in 1,000,000 up to 1 in 400,000).

Criticisms of the Methods of van den Bergh and various Suggestions for Alternative Tests.

Thannhauser and Andersen (1921) have found difficulty with the artificial standard solution used by van den Bergh for the colorimetric quantitative test. They have found that the standard solution of rhodanate of iron is reddish-violet in colour, whereas the test solution is more rose-coloured. They also draw attention to the fallacy from loss of pigment in the sediment after precipitation with alcohol, and state that this loss is not surprising since pure bilirubin is quite insoluble in alcohol. Nevertheless, the bulk of the bilirubin does remain in the alcoholic solution. These writers point out that azobilirubin is, like all azo-compounds, an indicator, which alters its colour according to variations in hydrogen-ion concentration. In the method described by van den Bergh there is no equality of the hydrogen-ion concentration in the two fluids which are compared, and this is the reason why the colours are not identical. Suggestions for improvement in technique are made, for which the original paper should be consulted.

Adler and Meyer (1920) also criticize the standard solution used by van den Bergh, and state that the only accurate comparative solution is one made from pure bilirubin.

Meulengracht (1921) has suggested the use, for clinical purposes only, of a very simple colorimetric method for the quantitative estimation of bilirubin.

His method is based on the inference that bilirubin is the only yellow colouring matter of importance likely to be present in blood-serum. Oxalated plasma is used for the test, and an apparatus similar to the Sahli haemoglobinometer is employed. The standard solution with which the plasma is compared, and diluted to equal, is made up of:

Bichromate of potash	0.05 gm.
Sulphuric acid	2 drops.
Distilled water	500 c.cm.

Haselhorst (1921) has suggested another simplified method. The van den Bergh technique is carried out in the usual way, but as a standard solution for comparison he employs a mixture of Bordeaux red and alcoholic methylene blue made up of an intensity equal to that of a 1 in 200,000 solution of pure azo-bilirubin.

Holzer and Mehner (1922) have carried out a comparative test on 150 patients using all of the suggested modifications given above, except the somewhat complicated methods described by Thannhauser and Andersen in their paper. Holzer and Mehner finally concluded that the original van den Bergh technique is the most reliable of all, provided it is carried out carefully with clean and dry apparatus. They state that dirty tubes and dirty pipettes may ruin the results, and the writer can fully confirm this.

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